

**The Development of Pot-Economical Strategies
for the Synthesis of Natural Products and Analogs**

By

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Abstract

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The development of atom-, redox-, step-, and pot-economical methods for the efficient synthesis of medicinal drugs, bioactive natural products and their synthetic analogs stands at the forefront of modern day organic synthesis and drug discovery. In particular, one-pot sequential operations are of prime importance due to their efficiency, versatility, and expediency in constructing advanced intermediates, polycyclic scaffolds and bioactive natural products. One-pot sequential protocols enable the formation of several bonds and stereocenters in a single reaction vessel, and minimize the need for workup and chromatographic procedures between intermediary steps, thus saving time and reducing chemical waste generation in multistep syntheses of bioactive target molecules.

Previous studies in our group have focused on the development and utilization of one-pot sequential protocols for the synthesis of (–)-tetrahydrolipstatin and strictifolione. The focus of this dissertation is the development and implementation of one-pot sequential operations for the streamlined syntheses of α,β -unsaturated macrocycles, bioactive natural products and their synthetic analogs. Chapter-1 is a literature review focused on recent application of one-pot sequential protocols in natural product and drug synthesis.

Chapter-2 is work carried out in the course of this dissertation that is focused on the synthesis of functionalized and structurally diverse α,β -unsaturated 14-membered macrocycles. A series of one-pot sequential protocols was developed for the synthesis of novel macrocycles bearing α,β -unsaturated chemotypes. The method highlights a phosphate tether-mediated approach to establish asymmetry, and consecutive one-pot sequential processes to access the macrocycles with minimal purification procedures. This library amenable strategy provided diverse macrocycles containing α,β -unsaturated carbon-, sulfur-, or phosphorus-based warheads.

Chapter-3 outlines our work on a pot-economical total synthesis of antifungal natural product Sch-725674 and structural analogs. The approach takes advantage of a number of one-pot sequential transformations, including a phosphate tether-mediated one-pot sequential RCM/CM/ chemoselective hydrogenation protocol, a one-pot tosylation/ acrylation sequence, and a one-pot sequential Finkelstein reaction/ Boord olefination/ acetonide deprotection procedure to streamline the synthesis route by reducing isolation and purification procedures, thus saving time. Overall, an asymmetric route has been developed that is efficiently accomplished in seven pots from phosphate (*S,S*)-triene and with minimal purification.

Chapter 4 describes our ongoing efforts toward the asymmetric total synthesis of (–)-13-desmetnyl-lyngbouilloside an unnatural analog of lyngbouilloside. The key reactions involved in the synthesis of 13-desmethyl-lyngbouilloside are one-pot sequential RCM/CM/ chemoselective hydrogenation, regio- and diastereoselective cuprate addition followed by tether removal, Pd-catalyzed reductive allylic

transposition, Roskamp homologation, Boeckman acylketen cyclization, Julia olefination and glycosylation. Thus far, we were able to accomplish the synthesis of macrolactone core of (–)-13-desmetnyl-lyngbouilloside. Further studies towards the completion of the molecule are underway. Chapter 5 is a compilation of the experimental work carried out in this dissertation.

*To my parents for loving me and supporting me
throughout this journey*

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Abbreviations

aq	aqueous
AcCl	acetyl chloride
AcOH	acetic acid
Bn	benzyl
BnBr	benzyl bromide
brsm	based on recovered starting material
9-BBN	9-Borabicyclo(3.3.1)nonane
BOPCl	bis(2-oxo-3-oxazolidinyl)phosphonic chloride
t-BuOH	t-Butanol
CHCl ₃	chloroform
CuI	copper iodide
cat.	catalytic
COSY	correlation spectroscopy
C	carbon
ClCH ₂ CO ₂ H	dimethylformamide
Cs ₂ CO ₃	cesium carbonate
Cl	chlorine
NaOAc	sodium acetate
Fmoc	fluorenylmethyloxycarbonyl chloride
CsCl	caesium chloride
Cbz	carboxybenzyl

CM	cross metathesis
CuBr	copper bromide
CuI	copper iodide
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-diazabicycloundec-7-ene
DBAD	Di-tert-butyl azodicarboxylate
DCM (CH ₂ Cl ₂)	dichloromethane
DCE	1,2-Dichloroethane
DIAD	diisopropyl azodicarboxylate
DIPEA/Hünig's base	<i>N,N'</i> -Diisopropylethylamine
DMAP	4-(dimethylamino)pyridine
DMF	dimethylformamide
Me ₂ SO ₄	dimethylsulfate
Et	ethyl
Et ₂ O	diethyl ether
EtOAc	ethyl acetate
EDC (EDCI)	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
G-I	Grubbs' first generation catalyst
G-II	Grubbs second-generation catalyst
GC	gas chromatography
HG-II	Hoveyda-Grubbs second generation catalyst
HRMS	high-resolution mass spectrometry

h	hours
HCl	hydrochloric acid
Hz	hertz
IR	infrared radiation
i-Bu	isobutyl
i-Pr	isopropyl
LiOH	lithium hydroxide
LiCl	lithium chloride
LCMS	liquid chromatography–mass spectrometry
M	molarity
MeCN	acetonitrile
H ₂ O ₂	hydrogen peroxide
Me	methyl
MeOH	methanol
MeI	methyl iodide
Mmol	millimole(s)
MOM	methoxymethyl-
MsCl	methanesulfonyl chloride
NaHCO ₃	sodium bicarbonate
NMO	<i>N</i> -methylmorpholine- <i>N</i> -oxide
NMR	nuclear magnetic resonance
NH ₃	ammonia

NaClO ₂	sodium chlorite
NaBH ₄	sodium borohydride
NIH	National Institute of Health
NaH ₂ PO ₄	monosodium phosphate
nBuLi	n-butyllithium
OMe	methoxy
<i>o</i> -NBSH	o-nitrobenzene sulfonyl hydrazine
PMB	para-methoxybenzyl
ppm	parts per million
Ph	phenyl
PCy ₃	tricyclohexylphosphine
PTSA	<i>p</i> -toluenesulfonic Acid
K ₂ CO ₃	potassium carbonate
RCM	ring closing metathesis
Rt/RT	room temperature
sat.	saturated
NaOtBu	sodium tert-Butoxide
NaHMDS	sodium hexamethyldisilazide
NaOH	sodium hydroxide
Na ₂ SO ₄	sodium sulfate
TBACl	tetrabutyl ammonium chloride
TBAF	tetrabutyl ammonium fluoride

TIPS	triisopropylsilyl-
TBDPS	tert-butyl(diphenyl)silyl-
TBS	tert-butyl(dimethyl)silyl-
TMSCl	trimethylsilyl chloride
TMSOTf	trimethylsilyl trifluoromethanesulfonate
PCC	pyridinium chlorochromate
Pd(OAc) ₂	palladium (II) acetate
Pd(OH) ₂	palladium hydroxide
TFA	trifluoroacetic acid
K ₃ PO ₄	tripotassium phosphate
PPh ₃	triphenylphosphine
tolSH	toluenethiol
TLC	thin layer chromatography
TiCl ₄	titanium tetrachloride
EtOH	ethanol
t-Bu	tert-butyl
Et ₃ N	triethylamine
THF	tetrahydrofuran
2,2-DMP	dimethoxypropane
PPTS	pyridinium p-toluenesulfonate
LLS	longest linear sequence
TSC	total step count

Yb(OTf) ₃	ytterbium (II) trifluoromethanesulfonate
TOS	target oriented synthesis
Si	silicon
IC ₅₀	inhibitory concentration at 50%
Me ₂ Zn	dimethylzinc
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
Boc	tert-butyloxycarbonyl
DOS	diversity oriented synthesis
NBS	<i>N</i> -bromosuccinimide
NaOAc•3H ₂ O	sodium acetate trihydrate
Ac ₂ O	acetic anhydride

Chapter 1

One-pot Sequential Protocols for the Synthesis of Medicinal Compounds, Natural Products and Analogs

1.1. Introduction

The development of atom-,¹ redox-,² step-,³ and pot-economical⁴ strategies to access advanced intermediates for the synthesis of medicinal drugs, bioactive natural products and analogs stands at the forefront of modern-day synthesis and drug discovery. In particular, one-pot reaction protocols are of prime importance due to their efficiency, versatility, and expediency in constructing densely functionalized advanced intermediates,^{5, 6} polycyclic ring systems⁷ and bioactive natural products.⁴ One-pot reaction protocols enable the formation of several bonds and stereocenters in a single reaction vessel. These efficient processes reduce the need for workup and chromatographic separations between intermediary steps, thus saving time and minimizing waste generation in multistep syntheses of bioactive target molecules.^{8, 9, 10} A basic keyword search using Sci-Finder unveils the historic development of one-pot reaction protocols over the past few decades.¹¹ The number of scientific reports containing the concept “one-pot reaction” has increased significantly between 1980 and 2015 (Figure 1.1b). Although, the number of articles containing the concept “one-pot reaction” steadily grew between 1980–2000, the last fifteen years (2000–2015) in the literature among the synthetic community has seen immense popularity of one-pot reaction protocols. Moreover, Hayashi and coworkers have recently developed methods, which enhance the number of reactions that can be performed in one-pot protocols, *vide infra*. This work has inspired efforts in this dissertation to develop chemistry aimed at the streamlined synthesis of macrocyclic natural products and their corresponding analogs via the use of a series of one-pot sequential protocols.

One-pot reaction protocols are broadly divided into two main categories *i.e* one-

pot multicomponent, whereby all components are added at the beginning domino/cascade reactions are a subset of this category and one-pot sequential reactions (components/reagents are added sequentially). Historically, one-pot processes such as Passerini¹² and Ugi reactions¹³ first reported in 1921 and 1959, respectively, have dominated the one-pot literature.

Figure 1.1a

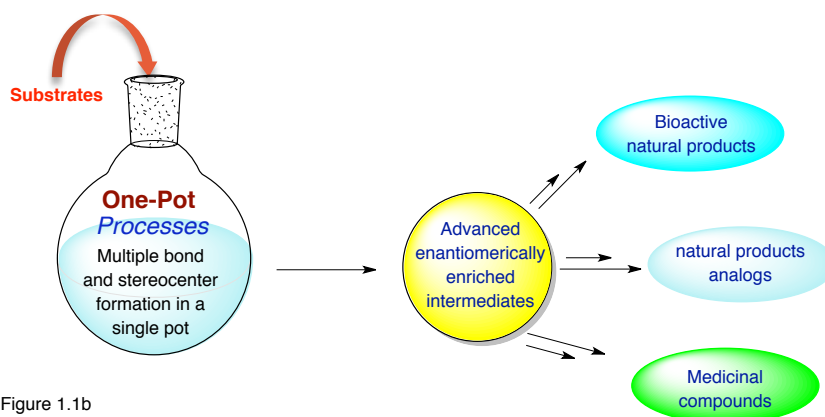


Figure 1.1b

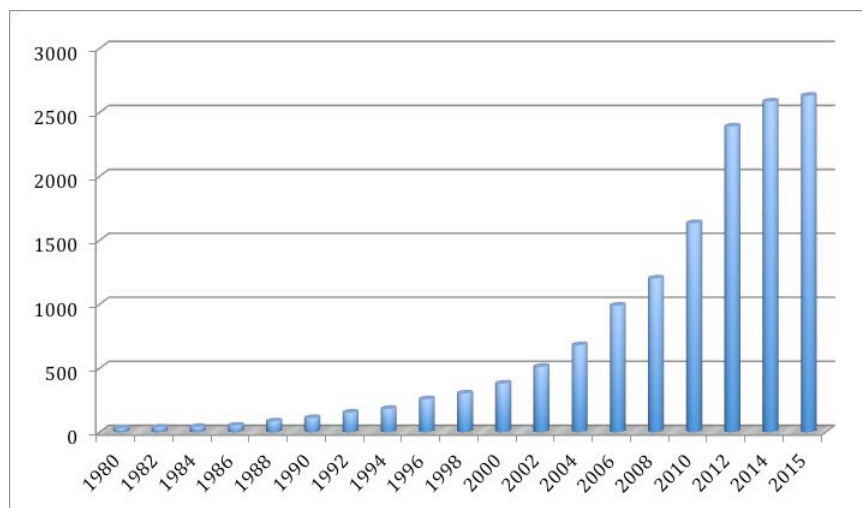


Figure 1.1. a) One-pot reaction protocols for the syntheses of natural products and medicinal compounds. b) Number of scientific reports containing the keyword “one-pot reaction” from 1980–2015. (Data were attained via keyword search using Sci-Finder.)

Tietze proposed the term “domino reactions” for one-pot processes and defined that the domino reactions are the processes that involve the formation of two or more

bonds (usually C–C bonds) under the same reaction conditions without the addition of additional reagents and catalysts, and in which the subsequent transformations occur as a consequence of the functionality formed in the prior reactions. A 2014 review on the concept of domino reactions by Tietze and coworkers (as well as earlier reviews), highlights the vast arsenal of tandem and cascade processes that have been developed for the total synthesis of natural products and analogs.¹⁴ Nicolaou described in his 2006 review titled “ Cascade Reactions in Total Synthesis” that these descriptions for the one-pot processes are comparatively interchangeable.¹⁵ One-pot reactions (domino/cascade reactions) are extensively studied and have been reviewed multiple times in the literature.^{4a-b,12,15,16} The second category known as “one-pot sequential reactions” is underexplored and recently started gaining popularity both in the synthetic community and in industry.

In 2007, Clarke and coworkers introduced the concept of combining Pot-, Atom- and Step-Economy (PASE) in organic synthesis, which refers to the completion of sequential reactions in a single flask without the need for workup and purification between steps.¹⁷ The authors suggested that PASE syntheses are green in nature as they have the potential to (i) reduce the number of synthetic pots, which in turn minimizes the number and amount of reagents needed, (ii) reduce the amount of solvents in reactions, workup, and chromatographic purifications, and (iii) reduce waste and contaminants generated from cleaning equipment and glassware.

Since 2009, the aforementioned elegant efforts by Hayashi and coworkers have been of particular note for the use of consecutive one-pot sequential procedures (*i.e* a series of one-pot protocols) to complete multi-reaction syntheses of (–)-oseltamivir,¹⁸

Dpp4-selective inhibitor ABT-341,¹⁹ prostaglandin A₁ and E₁ methyl esters,²⁰ (–)-horsfiline, (–) coerulescine²¹ and (*S*)-baclofen.²² Inspired by this body of work, Hanson and coworkers have utilized the "one-pot paradigm" in a number of phosphate tether-mediated one-pot sequential protocols for the syntheses of (–)-tetrahydrolipstatin,²³ strictifolione²⁴ and Sch-725674.²⁵ Moreover, they have applied this concept in the generation of diverse α,β -unsaturated 14-membered macrocycles bearing carbon-, sulfur- and phosphorus-based warheads.²⁶ It is the purpose of this chapter to compile a brief account of the recent literature on the use of one-pot sequential protocols for the synthesis of advanced intermediates,^{6,7} medicinal compounds,^{18,19,20} selected bioactive natural products and their corresponding analogs.

1.2. Development of one-pot sequential protocols by Clarke and coworkers

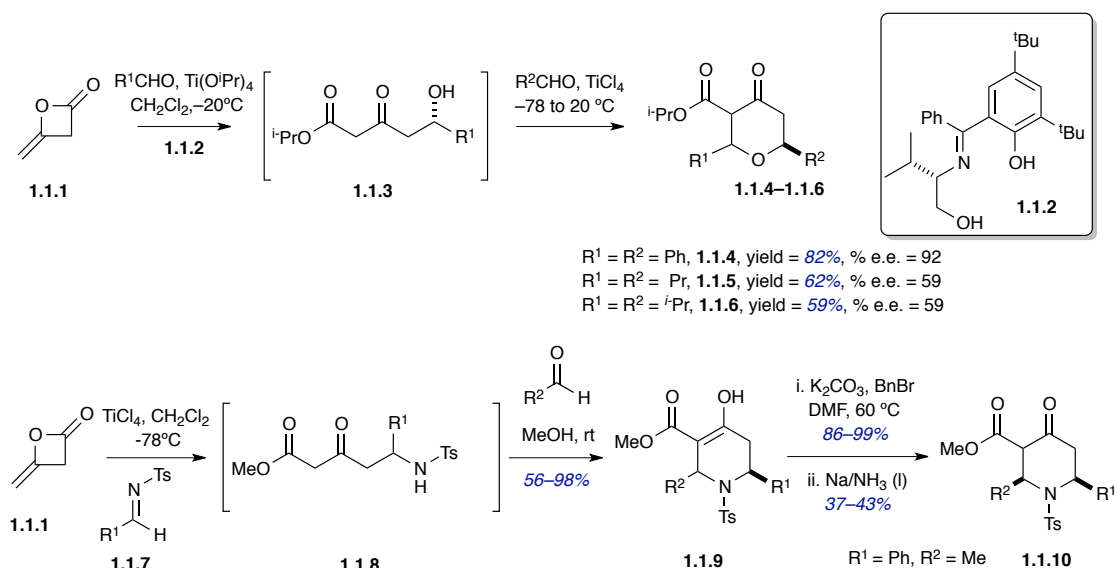
1.2.1. Syntheses of functionalized tetrahydropyran-4-ones and substituted piperid-4-ones using the Pot, Atom and Step Economy (PASE) principle

In 2007, Clarke and coworkers employed the PASE principle to synthesize a series of highly substituted tetrahydropyran-4-ones (THPs) (**1.1.4–1.1.6**) (Scheme 1.1).^{17a} These one-pot sequential processes began with a Lewis acid-catalyzed addition of diketene **1.1.1** to an aldehyde in the presence of Schiff base **1.1.2**. The resulting enantiomerically pure aldol adducts **1.1.3** subsequently underwent Knoevenagel condensation with a second aldehyde, followed by an intramolecular Michael reaction in the same pot to afford functionalized tetrahydropyran-4-ones (**1.1.4**). Taken collectively, the authors were able to synthesize highly substituted THPs (**1.1.4–1.1.6**) in moderate to good overall yields and good to excellent enantioselectivities (Scheme 1.1).

Similarly in 2008, Clarke and coworkers reported the synthesis of highly substituted piperid-4-ones **1.1.10** using a one-pot, four-component condensation approach

(Scheme 1.1).^{17d} The sequence involved Lewis acid (TiCl₄)-catalyzed diketene **1.1.1** addition to a tosyl imine **1.1.7** to furnish the aldol adduct **1.1.8**. The crude product was subsequently treated with one equivalent of aldehyde in MeOH to afford a *cis/trans*-diastereomeric mixture of substituted piperid-4-ones **1.1.9** in good yield. The mixture of diastereomers was efficiently converted to a single diastereomer of piperid-4-ones **1.1.10** by epimerization under basic conditions. The authors suggested that this robust method would enable access to a diverse range of substituted piperid-4-ones **1.1.10** in good yield by employing a variety of different coupling partners.

Scheme 1.1. PASE synthesis of tetrahydropyran-4-one and piperidines.



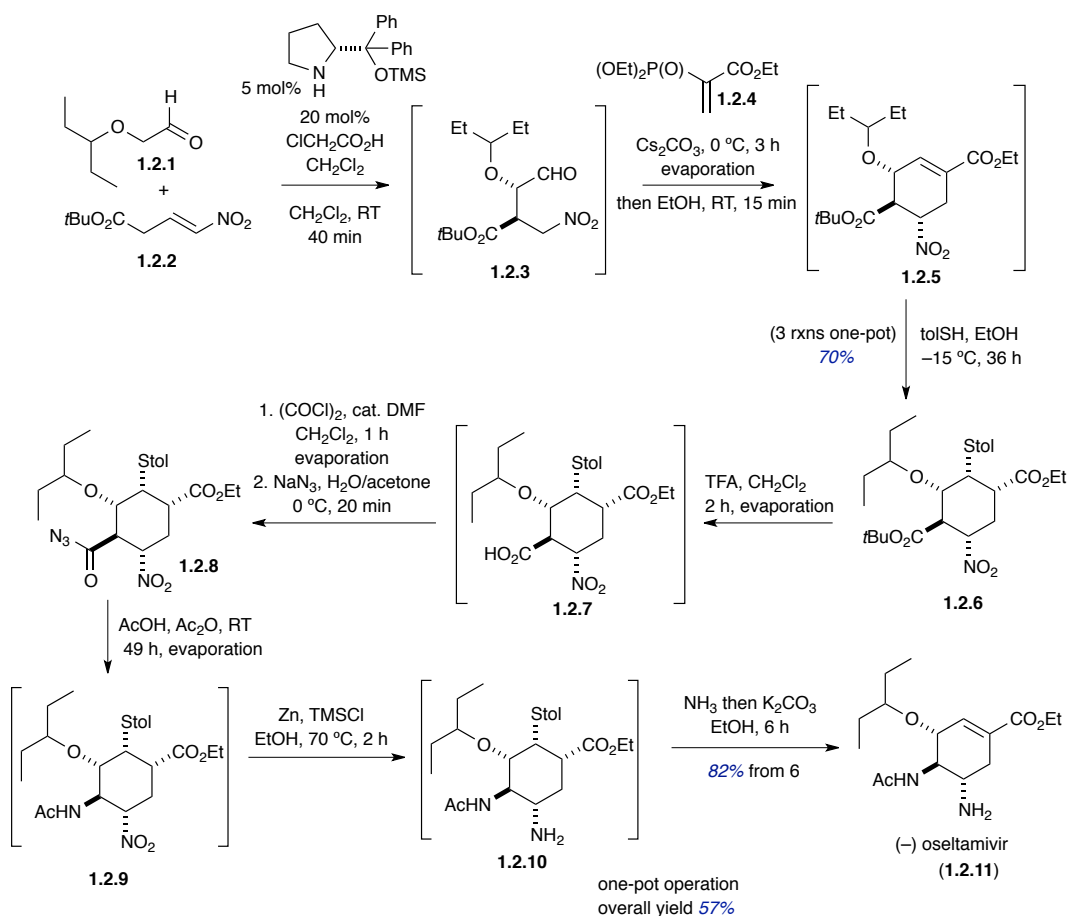
1.3. Application of one-pot sequential protocols in the synthesis of bioactive natural products and medicinal drugs by Hayashi and coworkers

1.3.1. Synthesis of (–)-oseltamivir via a sequence of three one-pot sequential operations

In 2009, Hayashi and coworkers reported the synthesis of (–)-oseltamivir utilizing three one-pot operations (Scheme 1.2).¹⁸ (–)-Oseltamivir phosphate (Tamiflu®) is a neuraminidase inhibitor, which is effectively used as a drug for the treatment of human

influenza.²⁷ The authors accomplished the synthesis of (–)-oseltamivir using a sequence of three one-pot processes requiring only one-purification procedure. The first one-pot operation began with an asymmetric organocatalytic Michael addition of aldehyde **1.2.1** to nitroalkene **1.2.2** using diphenylprolinol silyl ether as a catalyst,²⁸ furnishing the adduct **1.2.3** in quantitative yield and high enantioselectivity.

Scheme 1.2. *Synthesis of (–)-oseltamivir via three one-pot operations.*



Next, the authors performed a Michael reaction between **1.2.3** and vinylphosphonate **1.2.4**, followed by an intramolecular Horner-Wardsworth-Emmons (HWE) reaction, and subsequent conjugate addition of toluenethiol, which furnished the substituted

cyclohexane **1.2.6** in 70% yield over three reactions in one pot. The *tert*-butyl ester **1.2.6** obtained after purification was deprotected with trifluoroacetic acid (TFA), which afforded carboxylic acid **1.2.7**.

The crude carboxylic acid was transformed to the corresponding acyl azide **1.2.8** over a sequence of two reactions in one-pot consisting of addition of oxalyl chloride followed by sodium azide in aqueous acetone at 0 °C. The acyl azide **1.2.8** was subsequently converted to amide **1.2.9** via Curtius rearrangement by treating the azide **1.2.8** with acetic acid and acetic anhydride at room temperature. Next, the nitro group in **1.2.9** was reduced to an amine (**1.2.10**) using zinc and TMSCl in EtOH at 70 °C. Finally, the crude product **1.2.10** was treated with K₂CO₃ to enable the retro-Michael reaction of the thiol moiety affording (–)-oseltamivir (**1.2.11**) in 82% yield.

The salient features of Hayashi's (–)-oseltamivir synthesis include; i) a single pot assembly of a fully functionalized ethylcyclohexenecarboxylate intermediate **1.2.6** with required stereochemical configuration, ii) use of a second pot for the deprotection of *tert*-butyl ester, as well as transfer of the crude acid **1.2.7** to the next pot without further purification, iii) utilization of a sequence of three reactions in the third pot involving Curtius rearrangement/reduction of the nitro group to an amine/retro-Michael reaction of the thiol, which completed the synthesis of the target molecule. Overall, this efficient synthesis comprised of nine reactions, which were performed in a sequence of three one-pot sequential operations to accomplish the synthesis of (–)-oseltamivir from the commercially available nitroalkene **1.2.2** in 57% overall yield. In 2010 and 2011, Hayashi and coworkers further streamlined the synthesis of (–)-oseltamivir by developing a consecutive two-pot sequence that consisted of eleven reactions with 60% overall yield

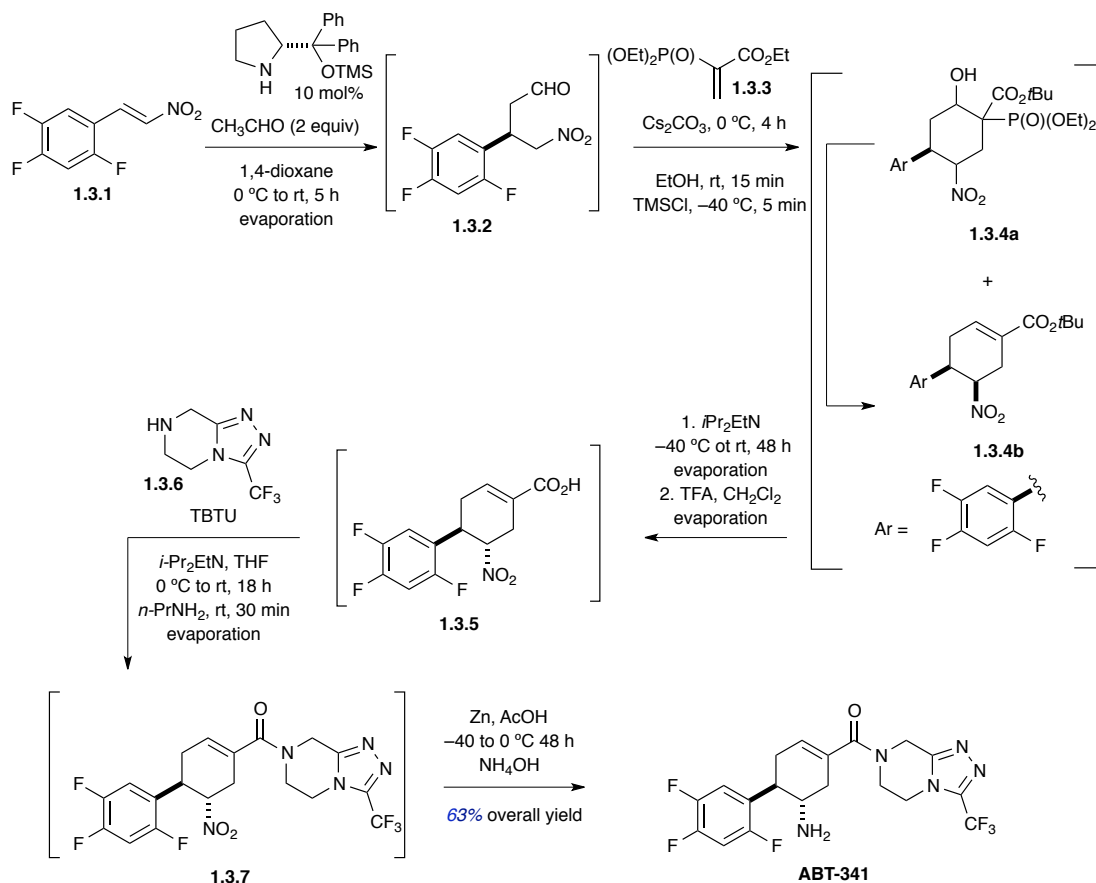
and only two workup and purification procedures.^{18b,c}

1.3.2. One-pot synthesis of ABT-341

In 2011, Hayashi and coworkers disclosed a one-pot synthesis of ABT-341,¹⁹ a potent orally bioavailable DPP4-selective inhibitor (Scheme 1.3). Similar to the synthesis of (–)-oseltamivir,¹⁸ the one-pot synthesis of ABT-341 commenced with an enantioselective Michael addition of an acetaldehyde to nitroalkene **1.3.1** in the presence of diphenylprolinol silyl ether as an organocatalyst to afford adduct **1.3.2**. The resulting nitroalkene **1.3.2** underwent a successive Michael addition with vinylphosphonate **1.3.3**, followed by a Horner–Wadsworth–Emmons reaction (HWE) reaction to afford the cyclized product **1.3.4a**. The successive reaction for the formation of chiral cyclohexene carboxylic acid **1.3.5** was the epimerization of the α position of the nitroalkane, which was not proceeding in the presence of Cs_2CO_3 .

In order to solve this problem, TMSCl was added to the crude reaction mixture, which reacted with the solvent (EtOH) to generate HCl . The in situ-generated HCl reacted with Cs_2CO_3 to provide insoluble CsCl . After quenching the Cs_2CO_3 , addition of $i\text{-Pr}_2\text{EtN}$ cleanly promoted the isomerization process, which was followed by *tert*-butyl ester deprotection using TFA to afford the cyclohexene carboxylic acid **1.3.5** with the desired stereochemistry. The crude carboxylic acid was subjected to *o*-(benzotriazol-1-yl)- N,N,N',N' -tetramethyluronium tetrafluoroborate (TBTU)-mediated coupling with amine **1.3.6** to furnish amide **1.3.7**. The nitro group in amide **1.3.7** was reduced to corresponding amine using Zn and AcOH . Overall, the synthesis of ABT-341 was completed in 63% yield over a sequence of nine reactions in one-pot.

Scheme 1.3. One-pot sequential protocol for the synthesis of ABT-341.

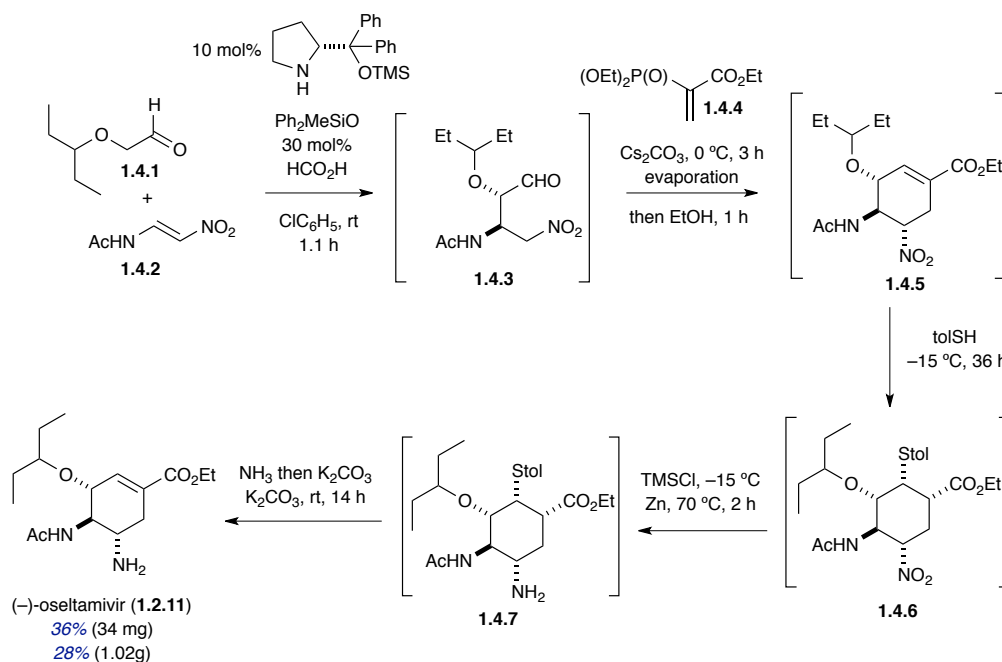


1.3.3. Synthesis of (–)-oseltamivir via a one-pot sequential operation

As a further refinement of one-pot sequential protocols, Hayashi and coworkers reported a one-pot synthesis of (–)-oseltamivir (**1.2.11**) in 2013.²⁹ This one-pot synthesis of **1.2.11** commenced with diphenylprolinol silyl ether-mediated asymmetric Michael reaction of α -alkoxyaldehyde **1.4.1** with *trans*-nitroalkene **1.4.2**. The rest of the synthesis of (–)-oseltamivir is a slight modification of the previously reported three-pot synthetic sequence by Hayashi and coworkers, which is discussed in detail in section 1.3.1 (Scheme 1.2). The advantages of the aforementioned one-pot sequential operations are that no solvent evaporation or change of solvents was needed, and that a single workup

and chromatographic purification was required for the synthesis of **1.2.11**. In addition, this one-pot procedure demonstrates the power of a carefully designed one-pot sequential protocol which enabled the synthesis of a stereochemically complex $\{(-)\text{-oseltamivir}\}$ on a gram scale (1.2 g) in 28% overall yield.

Scheme 1.4. One-pot synthesis of $(-)\text{-oseltamivir}$.

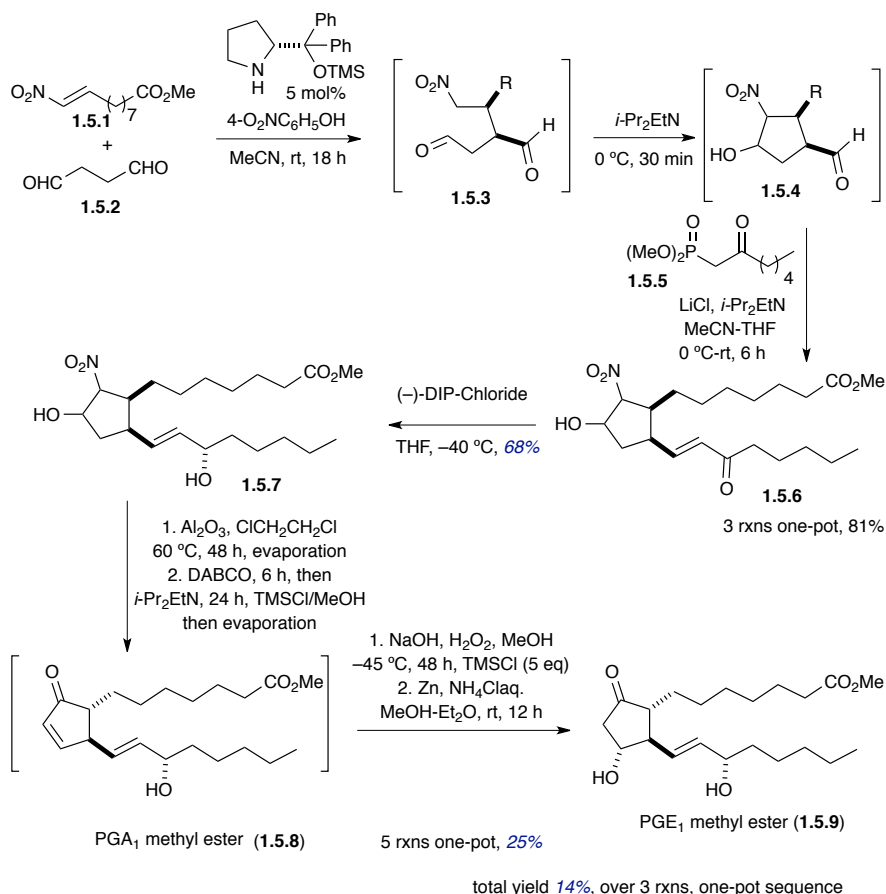


1.3.4. Synthesis of prostaglandin A₁ and E₁ methyl esters through a sequence of three one-pot sequential operations

Two years later, in 2013 Hayashi and coworkers reported an enantioselective total synthesis of prostaglandin A₁ (PGA₁) (**1.5.8**) and E₁ (PGE₁) methyl esters (**1.5.9**) in 25% and 14% overall yield, respectively (Scheme 1.5).²⁰ The forward synthesis began with organocatalytic asymmetric Michael addition of aldehyde **1.5.2** to nitroalkene **1.5.1** to furnish the aldehyde **1.5.3**. The crude product **1.5.3** was subsequently subjected to an intramolecular Henry reaction facilitated by *i*-Pr₂EtN,³⁰ which afforded the corresponding cyclopentanecarbaldehyde **1.5.4**. Next, the authors performed a sequential HWE reaction

of **1.5.4** with alkylphosphonate **1.5.5** in the same pot to afford the desired α,β -unsaturated ketone **1.5.6**.

Scheme 1.5. Three-pot synthesis of prostaglandin A_1 and E_1 methyl esters.



Diastereoselective reduction of the α,β -unsaturated ketone functionality in **1.5.6** using (–)-diisopinocampheyl chloroborane (DIPCI) afforded the alcohol **1.5.7** in 68% yield ($dr = 96:4$), completing the skeleton of prostaglandin with all the necessary carbon atoms. It is noteworthy to mention that protection of hydroxyl group in **1.5.7** was not required, thus avoiding additional protection/deprotection reactions. The resulting alcohol **1.5.7** was subjected to a one-pot sequential dehydration by using acidic alumina and double bond isomerization to afford the 2-nitrocyclopentene. The crude 2-nitrocyclopentene was converted to the corresponding PGA_1 methyl ester (**1.5.8**) via a

novel transformation of the nitro group in **1.5.7** to a carbonyl functionality using Nef reaction conditions.³¹ Subsequently, the authors epimerized the α -side chain from *cis* to *trans* orientation with respect to the ω -side chain in **1.5.7**. Without quenching, the reaction mixture was neutralized with TMSCl and then a base-mediated epoxidation was performed. The resulting epoxy ketone was subsequently treated with Zn and aqueous NH₄Cl to afford the PGE₁ methyl ester (**1.5.9**) in 14% overall yield.

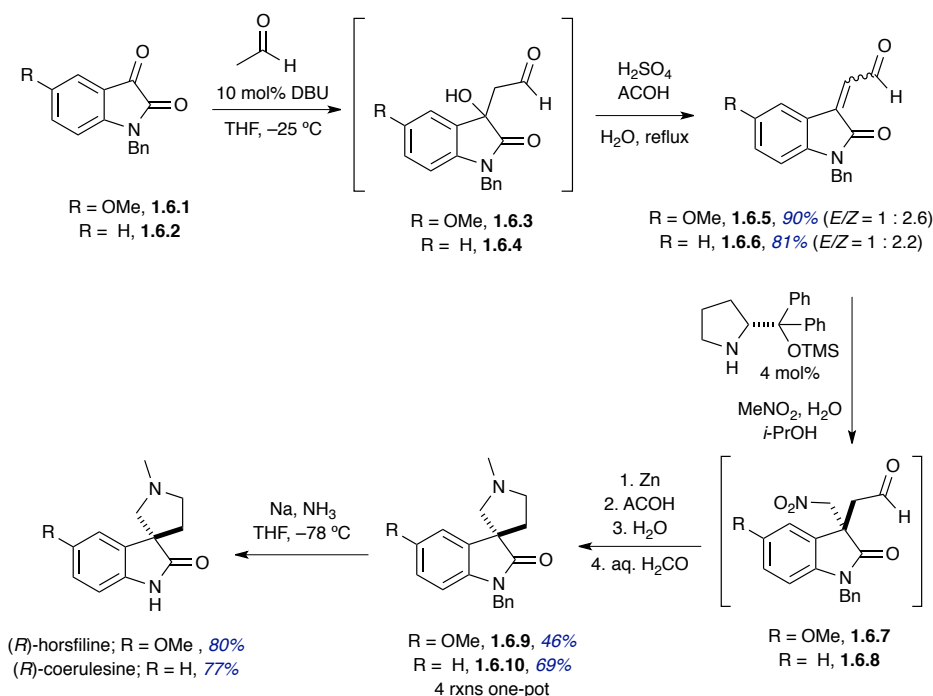
In summary the syntheses of both PGA₁ (**1.5.8**) and PGE₁ methyl esters (**1.5.9**) were accomplished in three one-pot sequential operations from inexpensive and simple starting materials. This short synthetic route involved only three isolations and three purification events, which greatly facilitated the syntheses of both the prostaglandin A₁ (**1.5.8**) and E₁ methyl ester and (**1.5.9**).

1.3.5. Synthesis of (–)-horsfiline and (–)-coerulescine alkaloids

The next year, in 2014, Hayashi and coworkers reported the synthesis of (–)-horsfiline and (–)-coerulescine alkaloids via three one-pot sequential operations in 33% and 46% overall yields, respectively (Scheme 1.6).²¹ The forward synthesis commenced with a DBU-catalyzed aldol reaction of commercially available isatin derivatives **1.6.1** and **1.6.2** with formaldehyde and was followed by dehydration to afford an *E/Z* mixture of olefins **1.6.5** and **1.6.6** in 90% and 81% yields, respectively. The aldehydes **1.6.5** and **1.6.6** were next subjected to an enantioselective conjugate addition of nitromethane to furnish the corresponding Michael adducts **1.6.7** and **1.6.8** with all quaternary-carbon stereogenic centers. Zn was added to the crude reaction mixture and was followed by AcOH and water to reduce the nitro groups in **1.6.7** and **1.6.8** to the corresponding amines. The amines subsequently underwent intramolecular reductive

amination to afford the pyrrolidinone spirocycles. Next, *N*-methyl substitution was carried out by simple addition of formaldehyde to the crude reaction mixture to afford **1.6.9** and **1.6.10** in moderate to good yields. Finally, benzyl deprotection with Na/NH₃ at -78 °C completed the syntheses of (-)-horsfiline and (-)-coerulescine in a three-pot sequence with 33% and 46% overall yields, respectively.

Scheme 1.6. *Three-pot synthesis of (-)-horsfiline and (-)-coerulescine alkaloids.*

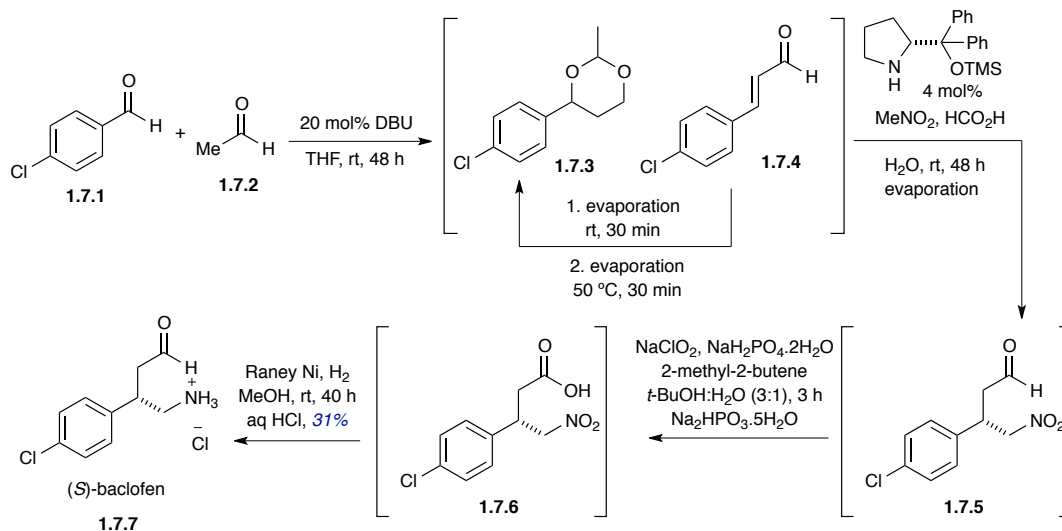


1.3.6. One-pot synthesis of (*S*)-baclofen

In 2016, Hayashi and coworkers accomplished the synthesis of (*S*)-baclofen (**1.7.7**) from commercially available starting materials **1.7.1** and **1.7.2** over a sequence of four reactions in one-pot (Scheme 1.7).²² The one-pot sequential operation began with DBU-catalyzed aldol condensation between *p*-chlorobenzaldehyde **1.7.1** and acetaldehyde **1.7.2**, which afforded the corresponding α,β -unsaturated aldehyde **1.7.4** with acetal **1.7.3** as a side product. The side product **1.7.3** was converted back to the

desired aldehyde **1.7.4** via retro-acetalization and dehydration reactions at 50 °C. The crude product **1.7.4** was subjected to organocatalytic asymmetric Michael reaction at room temperature to afford the nitroalkane **1.7.5**. Subsequent transformations were performed in the same pot: Karus-Pinnick oxidation³² afforded the carboxylic acid **1.7.6** and Raney Ni reduced the nitro group in **1.7.6**, completing the synthesis of (*S*)-baclofen (**1.7.7**) in 31% yield in one-pot.

Scheme 1.7. One-pot synthesis of the (*S*)-baclofen (**1.7.7**).

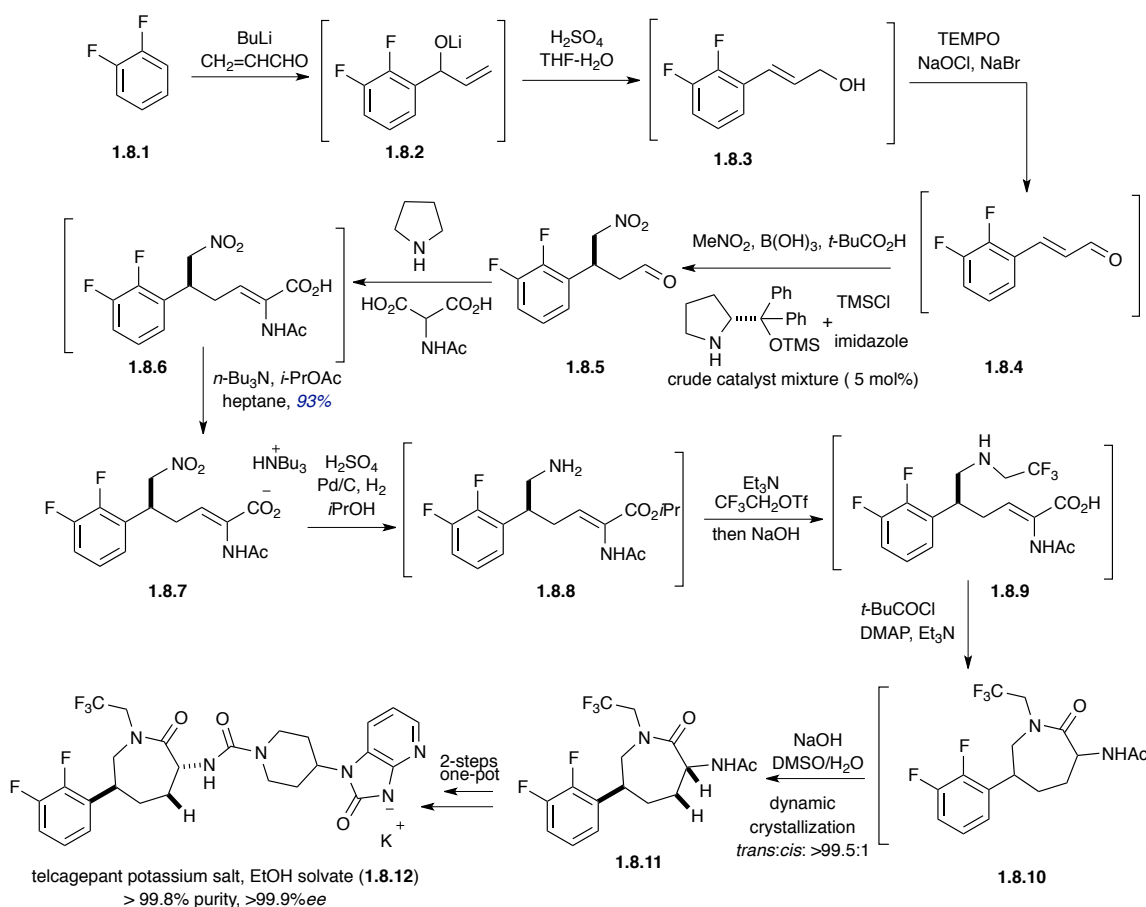


1.4. Application of one-pot sequential protocols for the synthesis of telcagepant

In 2010, researchers at Merck Research Laboratories reported a pot-economical synthesis of telcagepant, a CGRP-receptor antagonist³³ for the treatment of migraines.³⁴ The authors accomplished the synthesis of the crucial intermediate **1.8.7** via a three-step sequence consisting of two one-pot sequential operations (Scheme 1.8). The first one-pot operation involved four reactions to enable the synthesis of aldehyde **1.8.5**. The synthesis began with 1,2-addition of acrolein to commercially available 1,2-difluorobenzene **1.8.1** to furnish alcohol **1.8.2**. The crude alcohol was treated with H₂SO₄ to provide the

corresponding cinnamyl alcohol **1.8.3**. The crude product **1.8.3** was subsequently converted to the corresponding α,β -unsaturated aldehyde **1.8.4** using TEMPO oxidation and the resulting aldehyde was subsequently subjected to an asymmetric Michael reaction using nitromethane to afford the aldehyde **1.8.5** in one-pot with 48% overall yield (88% av/rxn). Next, the authors subjected the aldehyde **1.8.5** to the Doebner-Knoevenagel reaction³⁵ to afford the homologated enamine **1.8.6**, which was isolated as the tributylammonium salt **1.8.7** using *n*-Bu₃N and *i*-PrOAc in 93% yield.

Scheme 1.8. Pot-economical synthesis of telcagepant.



Upon successful synthesis of the core chiral framework **1.8.7**, the authors applied a second one-pot sequence involving reduction of the nitro group in **1.8.7** to an amine

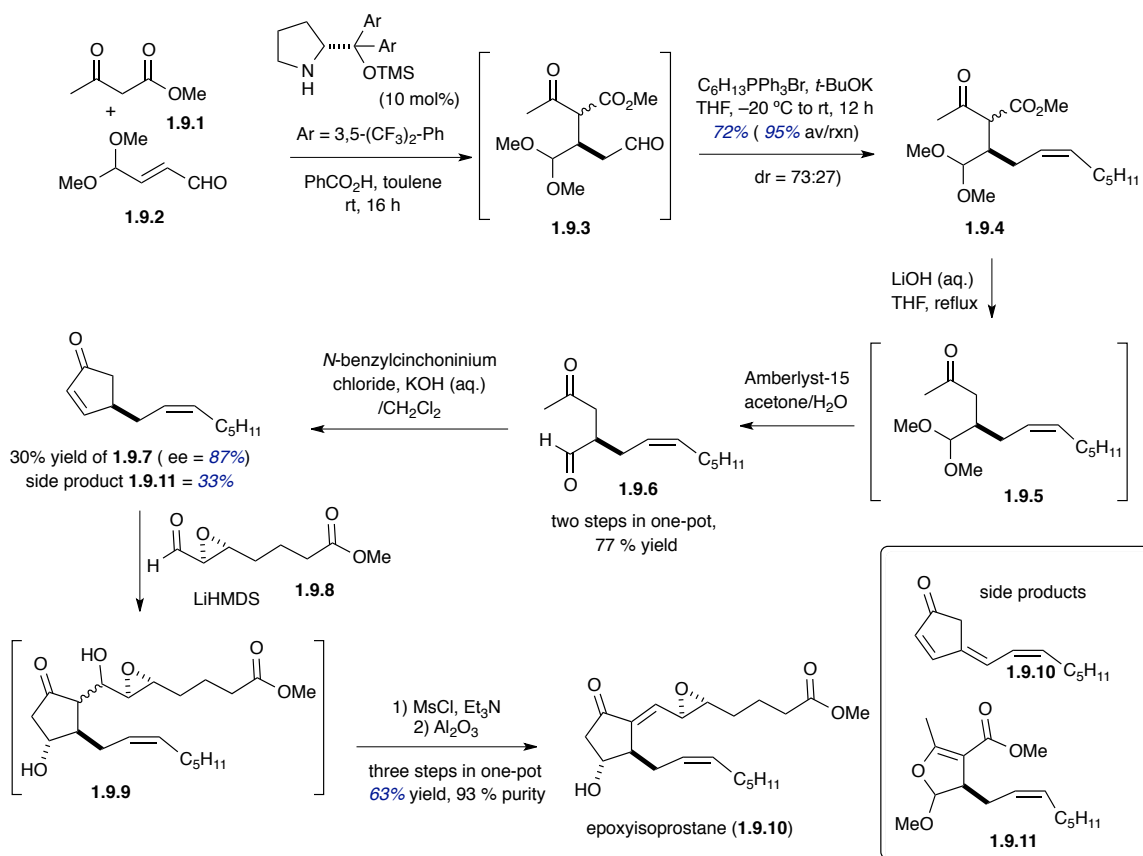
followed by trifluoroethylation of the resulting crude amine **1.8.8**. Subsequent hydrolysis of the ester functionality in **1.8.8** furnished carboxylic acid **1.8.9**. The crude product **1.8.9** was cyclized to produce the substituted ϵ -lactam **1.8.11** in 73% overall yield (*dr*: 95.5:1). The diastereoselectivity of the newly generated centers in **1.8.11** was controlled by dynamic epimerization/crystallization. The synthesis of telcagepant (**1.8.12**) was completed according to known literature procedures in a one-pot, two-step reaction sequence in 79% yield.³⁴ Throughout the synthesis of this therapeutic agent (telcagepant), only three intermediates were isolated, and no chromatographic procedures were necessary.

1.5. One-pot sequential protocol in the enantioselective total synthesis of epoxyisoprostanes

In 2015, Lu and coworkers developed a pot-economical approach for the stereoselective synthesis of epoxyisoprostanes (Scheme 1.9).³⁶ Toward this goal, the forward synthesis began with a one-pot sequential organocatalytic Michael reaction of methyl acetoacetate **1.9.1** with fumaraldehyde **1.9.2** to afford aldehyde **1.9.3**. The crude aldehyde was subsequently subjected to Wittig olefination reaction to afford alkene fragment **1.9.4** with 72% yield in one-pot. Olefin **1.9.4** was subjected to a second one-pot reaction sequence consisting of hydrolysis of the methyl ester in **1.9.4**, followed by decarboxylation of the resulting β -ketoacid to afford ketone fragment **1.9.5**. The acetal protecting group in crude **1.9.5** was deprotected using Amberlyst-15 to furnish ketoaldehyde **1.9.6** in 77% yield via two reactions in one-pot with 99% *ee*. The ketoaldehyde **1.9.6** was subjected to an intramolecular aldol condensation reaction using *N*-benzylcinchoninium chloride to afford the cyclopentenone **1.9.7** in 30% yield. The

resulting enone **1.9.7** was subjected to a one-pot, three-reaction sequence consisting of an intermolecular aldol reaction to install the side chain **1.9.8**,³⁷ mesylation, and *trans*-selective elimination to afford target molecule **1.9.10** in 63 % yield.

Scheme 1.9. *Enantioselective total synthesis of epoxyisoprostanes.*

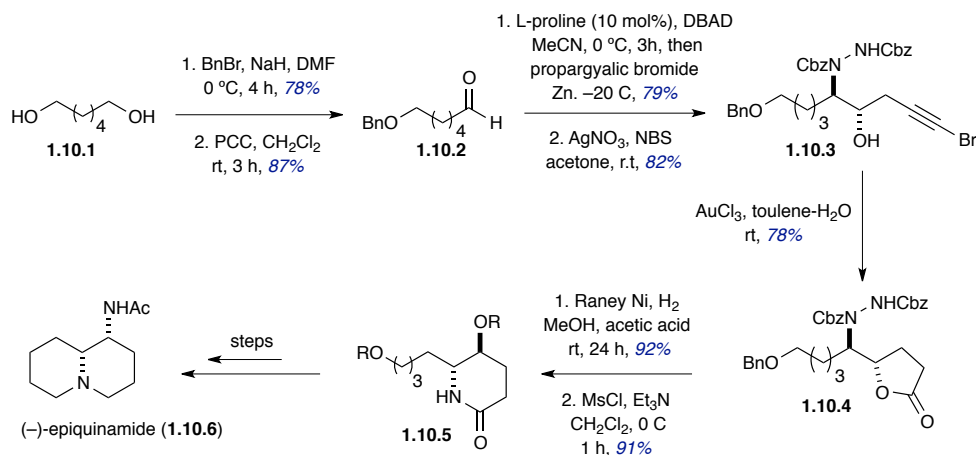


1.6. Application of one-pot sequential L-proline-catalyzed, α -amination/propargylation in the synthesis of (–)-epiquinamide

In 2016, Sudalai and coworkers reported an enantioselective formal total synthesis of (–)-epiquinamide (**1.10.6**) (Scheme 1.10).³⁸ The forward synthesis of **1.10.6** commenced with monobenzoylation of commercially available 1,6-hexanediol **1.10.1** followed by a selective oxidation of the unprotected alcohol in **1.10.1** using PCC to afford the aldehyde fragment **1.10.2** in 87% yield. Next, the authors performed an L-

proline-catalyzed one-pot sequential α -amination/propargylation reaction to afford the *anti*-amino alcohol in 79% yield. The resulting amino alcohol was brominated with NBS to furnish alkyne bromide **1.10.3**. Intramolecular hydroalkoxylation³⁹ of **1.10.3** using AuCl_3 as a catalyst in toluene/water afforded γ -butyrolactone **1.10.4** in 78% yield. The γ -butyrolactone was treated with Raney Ni and H_2 in MeOH, which led to cleavage of the N–N bond with simultaneous deprotection of the benzyl group. The resulting free amine underwent intramolecular opening of the lactone to generate a stable six-membered lactam, which was subsequently mesylated to afford the dimesylated fragment **1.10.5** in 91% yield. Advanced fragment **1.10.5** was converted to the final natural product (–)-epiquinamide (**1.10.6**) as reported in the literature.⁴⁰

Scheme 1.10. A formal enantioselective synthesis of (–)-epiquinamide using a one-pot sequential α -amination/propargylation sequence.

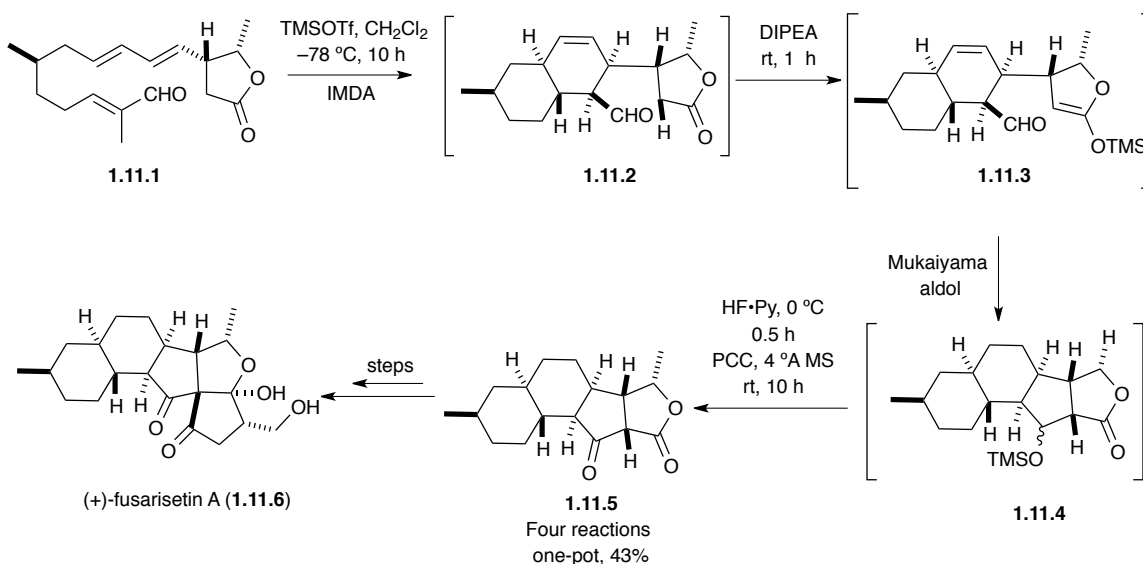


1.7. Enantioselective synthesis of (+)-fusarisetin A

In 2016, Zhang and coworkers reported a concise, asymmetric total synthesis of (+)-fusarisetin A (**1.11.6**) (Scheme 1.11).⁴¹ Toward this goal, the authors developed a one-pot, four-reaction sequence involving intramolecular Diels–Alder (IMDA)

reaction/Mukaiyama aldol/desilylation/oxidation, which efficiently afforded the tetracyclic core **1.11.5** of the natural product **1.11.6**. The forward synthesis of fusarisetin A began with the synthesis of intermediate **1.11.1** from known starting material in 3 linear steps.⁴¹ The triene **1.11.1** was subjected to an IMDA reaction using TMSOTf as Lewis acid to afford the aldehyde fragment **1.11.2**. The crude aldehyde was subsequently subjected to a Mukaiyama-aldol reaction to generate tetracyclic compound **1.11.4**. Without further purification, the tetracyclic compound was converted to lactone **1.11.5** via a sequential treatment with HF•Py at 0 °C and PCC at room temperature. Overall, tetracyclic lactone intermediate **1.11.5** was obtained in a one-pot process consisting of four reactions with 43% overall yield. Purified tetracyclic lactone intermediate **1.11.5** was converted to (+)-fusarisetin A after a few additional synthetic transformations.⁴¹

Scheme 1.11. An enantioselective total synthesis of (+)-fusarisetin A.



1.8. Phosphate tether-mediated one-pot sequential protocols for the synthesis of polyol containing bioactive natural products by Hanson and coworkers

As part of an ongoing program, recent efforts in the Hanson group are devoted to the development of one-pot sequential processes for the syntheses of polyol-containing intermediates, 1,3-diol-containing bioactive natural products, and their corresponding analogs (Figure 1.2).

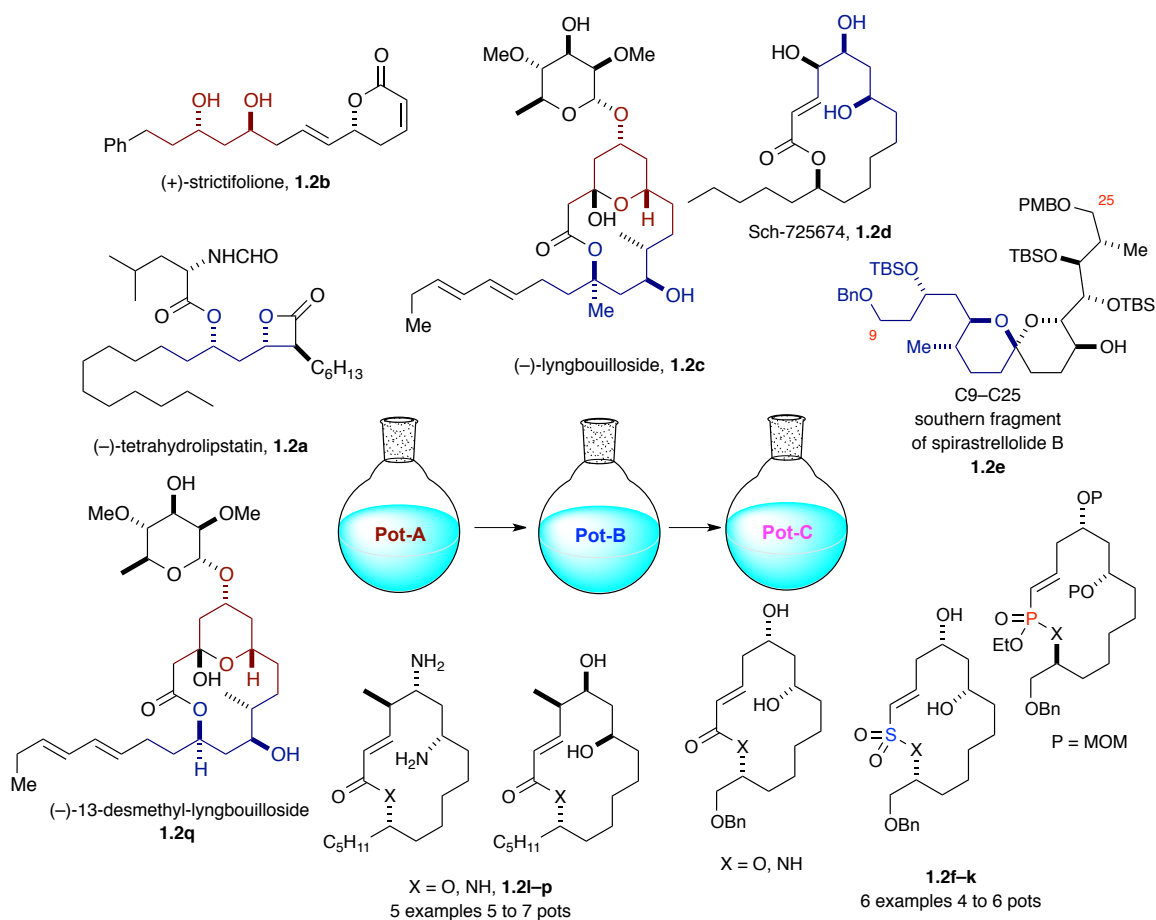


Figure 1.2. Phosphate tether-mediated one-pot sequential processes for the syntheses of bioactive natural products and corresponding analogs.

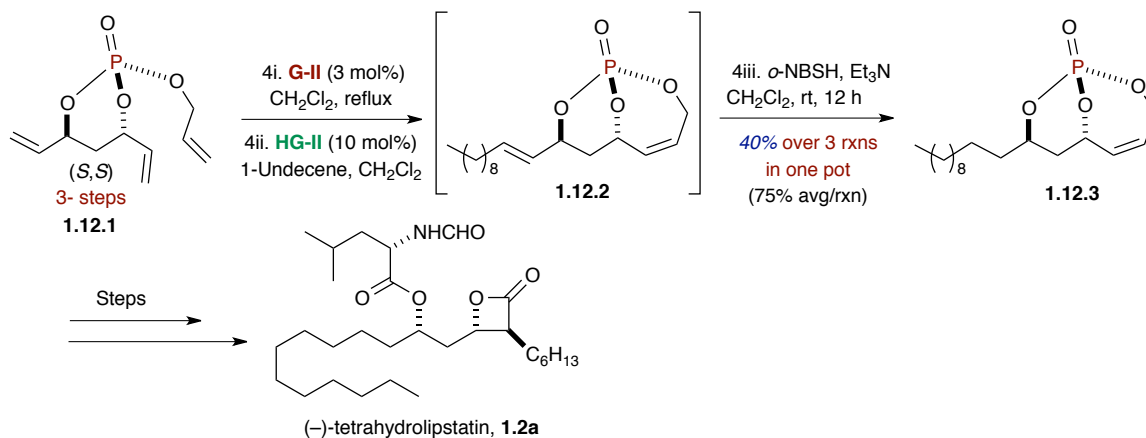
To date, one-pot sequential protocols have been successfully employed in the synthesis of (-)-tetrahydrolipstatin (**1.2a**, anti-obesity drug),²³ (+)-strictifolione (**1.2b**, antifungal),²⁴ the macrolactone core of the originally assigned structure of lyngbouilloside (**1.2c**),⁴² and

Sch-725674 (**1.2d**, antifungal) (Figure 1.2).²⁵ More recently, we reported an efficient synthesis of the C9–C25 subunit of spirastrellolide B (**1.2e**)⁴³ and a modular synthesis of a diverse range of functionalized novel α,β -unsaturated macrocycles (**1.2f–k**)²⁶ using one-pot sequential operations. In addition, we have implemented one-pot sequential operations in the syntheses of simplified analogs of Sch-725674 (**1.2l–p**) and 13-desmethyl-lyngbouilloside (**1.2q**) (Figure 1.2).

1.8.1. Application of one-pot sequential operations in the total synthesis of (–)-tetrahydrolipstatin

In 2010, Hanson and coworkers reported a concise synthesis of (–)-tetrahydrolipstatin (an anti-obesity drug) in 11 linear steps starting from readily prepared (*S,S*)-triene **1.12.1**⁴⁴ (Scheme 1.12).²³ In this efficient synthesis, the authors employed a phosphate tether-mediated one-pot sequential protocol. The sequence consisted of ring-closing metathesis, cross metathesis, and chemoselective hydrogenation (RCM/CM/“H₂”)⁶ reactions for the synthesis of bicyclic phosphate **1.12.3** from readily prepared (*S,S*)-triene **1.12.1** and commercially available 1-undecene as a CM partner. This one-pot sequence began with an RCM reaction of (*S,S*)-triene **1.12.1** using **HG-II** catalyst⁴⁵ (3 mol%) in refluxing CH₂Cl₂, which afforded the bicyclic phosphate. The crude product was subsequently subjected to a CM reaction using the **HG-II** catalyst (10 mol%) and 1-undecene CM partner to afford the bicyclic phosphate **1.12.2**. Without further purification and solvent change, the CM adduct **1.12.2** was subjected to chemoselective reduction of the external olefin in **1.12.2** by using *o*-NBSH and Et₃N (2mL/1g of *o*-NBSH). This one-pot three-reaction sequence furnished the bicyclic phosphate **1.12.3** in 40% yield (75% av/rxn). The purified bicyclic phosphate **1.12.3** served as an advanced intermediate for the synthesis of (–)-tetrahydrolipstatin (**1.12.4**).

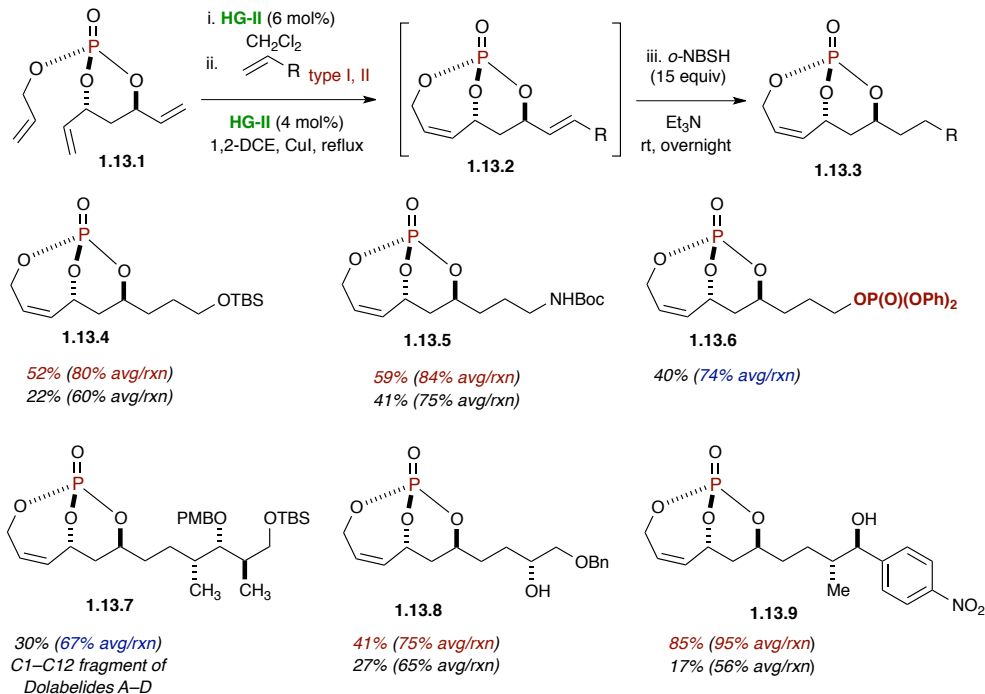
Scheme 1.12. Application of one-pot sequential RCM/CM/“H₂” protocol in the synthesis of (–)-tetrahydrolipstatin, **1.2a**.



1.8.2. Application of one-pot sequential RCM/CM/“H₂” protocol for the syntheses of advanced polyols subunits

To extend the applicability of the aforementioned phosphate tether-mediated one-pot sequential RCM/CM/“H₂” protocol, Hanson and co-workers were focused to optimize the reaction conditions for this efficient one-pot process to obtain better yields for the final products (Scheme 1.13).⁶ In this regard, the authors screened different solvents, catalysts, additives, and a variety of type I, II and III olefins for CM. After investigating various reaction conditions, moderate to good yields of the final products **1.13.4–1.13.9** were obtained for the one-pot sequential RCM/CM/“H₂” operation by using **HG-II**, freshly freeze-degas-thawed (FDT) DCM and DCE as solvents. Overall, this one-pot, three-reaction protocol can be utilized to streamline the syntheses of 1,3-skipped-polyol-containing scaffolds, bioactive natural products, and their corresponding analogs.

Scheme 1.13. One-pot sequential RCM/CM/hydrogenation.

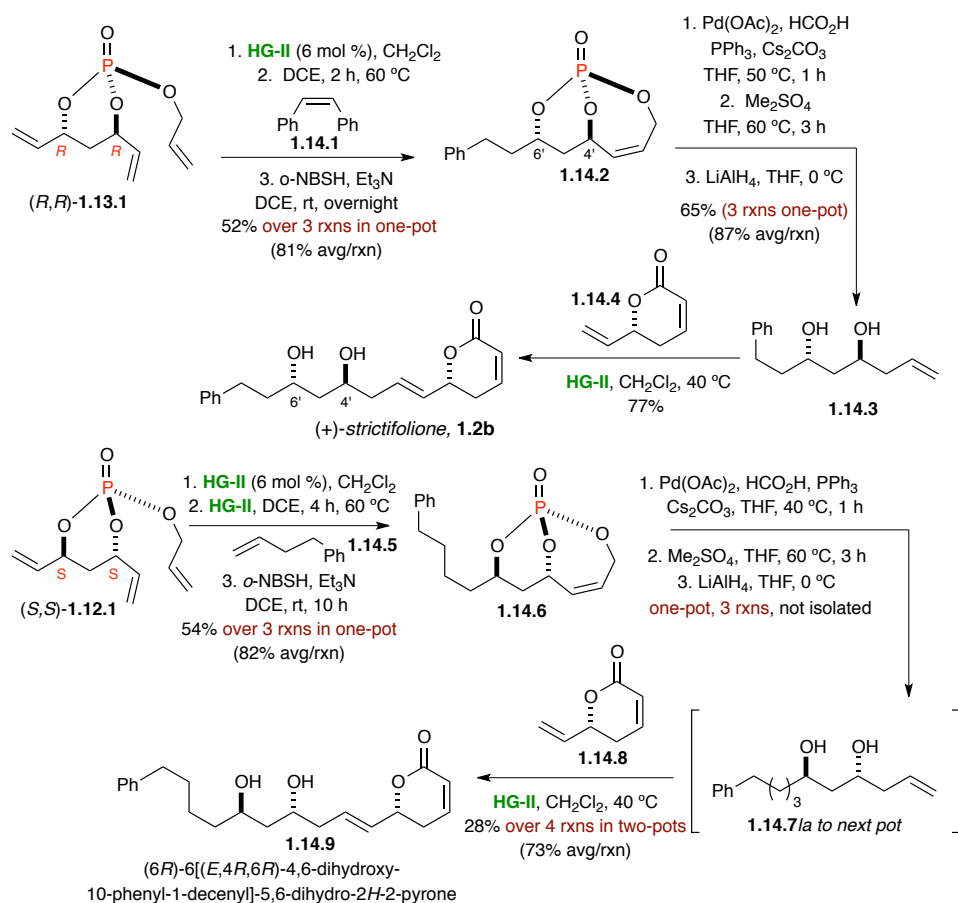


1.8.3. Asymmetric total synthesis of (+)-strictifolione via three one-pot sequential protocols

In 2014, Hanson and coworkers developed a pot-economical and library amenable approach for the asymmetric total synthesis of (+)-strictifolione (**1.2b**) and a related natural product (**1.14.9**) (Scheme 1.14).²⁴ The forward syntheses of **1.2b** and **1.14.9** began with the synthesis of bicyclic phosphates **1.14.2** and **1.14.6** via one-pot sequential RCM/CM/“ H_2 ”⁶ protocol from the corresponding phosphate triester-(*R,R*)-**1.13.1** and -(*S,S*)-**1.12.7**,⁴⁴ respectively. The bicyclic phosphates **1.14.2** and **1.14.6** were subsequently subjected to another one-pot sequential Pd-catalyzed, reductive allylic transposition/methylation/tether removal protocol to afford advanced 1,3-*anti* diol fragments **1.14.3** and **1.14.7**, respectively. The resulting diols **1.14.3** and **1.14.7** were transferred via cannula to the next pot without further purification. The solvent was evaporated and the CM partner **1.14.4** or **1.14.8** was introduced as a solution in DCE

followed by addition of the **HG-II** catalyst. The CM reaction afforded the final natural products **1.2b** and **1.14.9** in moderate to good yields. Overall, both natural products were efficiently accessed in three one-pot sequential operations from readily prepared phosphate triesters **1.13.1** and **1.12.1**, respectively.

Scheme 1.14. Three-pot synthesis of (+)-strictifolione and a related natural product.

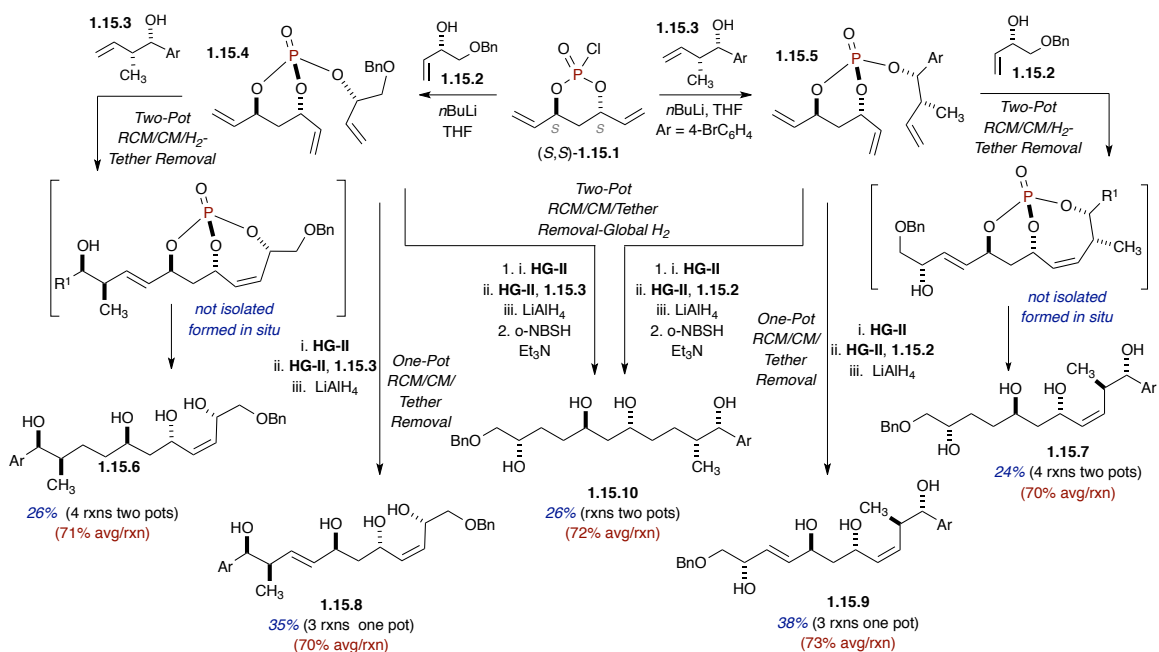


1.8.4. Syntheses of complex polyol containing scaffolds via one-pot sequential RCM/CM/“H₂” followed by reductive tether removal

In 2014, Hanson and coworkers developed a divergent, efficient and modular approach for the syntheses of polyol-containing scaffolds **1.15.6–1.15.10**.⁵ The key reactions involved in the syntheses of these polyols were a phosphate tether-mediated

one-pot sequential RCM/CM/“H₂” operation and a reductive tether removal (Scheme 1.15). The divergent aspect of this method was introduced by simply switching of CM partners **1.15.2** and **1.15.3** in the cross metathesis reactions to accomplish the syntheses of five different polyols subunits **1.15.6–1.15.10** starting from the three coupling partners **1.15.1**, **1.15.2** and **1.15.3**. As shown in Scheme 1.15, coupling of mono-chlorophosphate (*S,S*)-**1.15.1** with alcohol **1.15.3** furnished the phosphate triester (*S,S*)-**1.15.4**.

Scheme 1.15. *Synthesis of stereodiverse polyols via phosphate tether-mediated one-, two-pot sequential RCM/CM/reduction protocol.*



The resulting triene-(*S,S*)-**1.15.4** was further diversified by using two one-pot sequential processes: one-pot RCM/CM/“H₂” protocol and reductive tether removal to afford the tetraol subunit **1.13.6** in 26% yield over two-pots (4 reactions, 71% av/rxn). Accordingly, triene **1.15.5** was coupled with alcohol **1.15.2** through a one-pot sequential RCM/CM/“H₂” operation, followed by reductive tether removal using LiAlH₄ to generate polyol **1.15.7** in 24% yield over two-pots and four reactions (70% average per reaction).

In similar fashion, the authors were able to synthesize the polyol subunits **1.15.8–1.15.10** utilizing a one-pot sequential RCM/CM/“H₂” followed by phosphate tether removal.

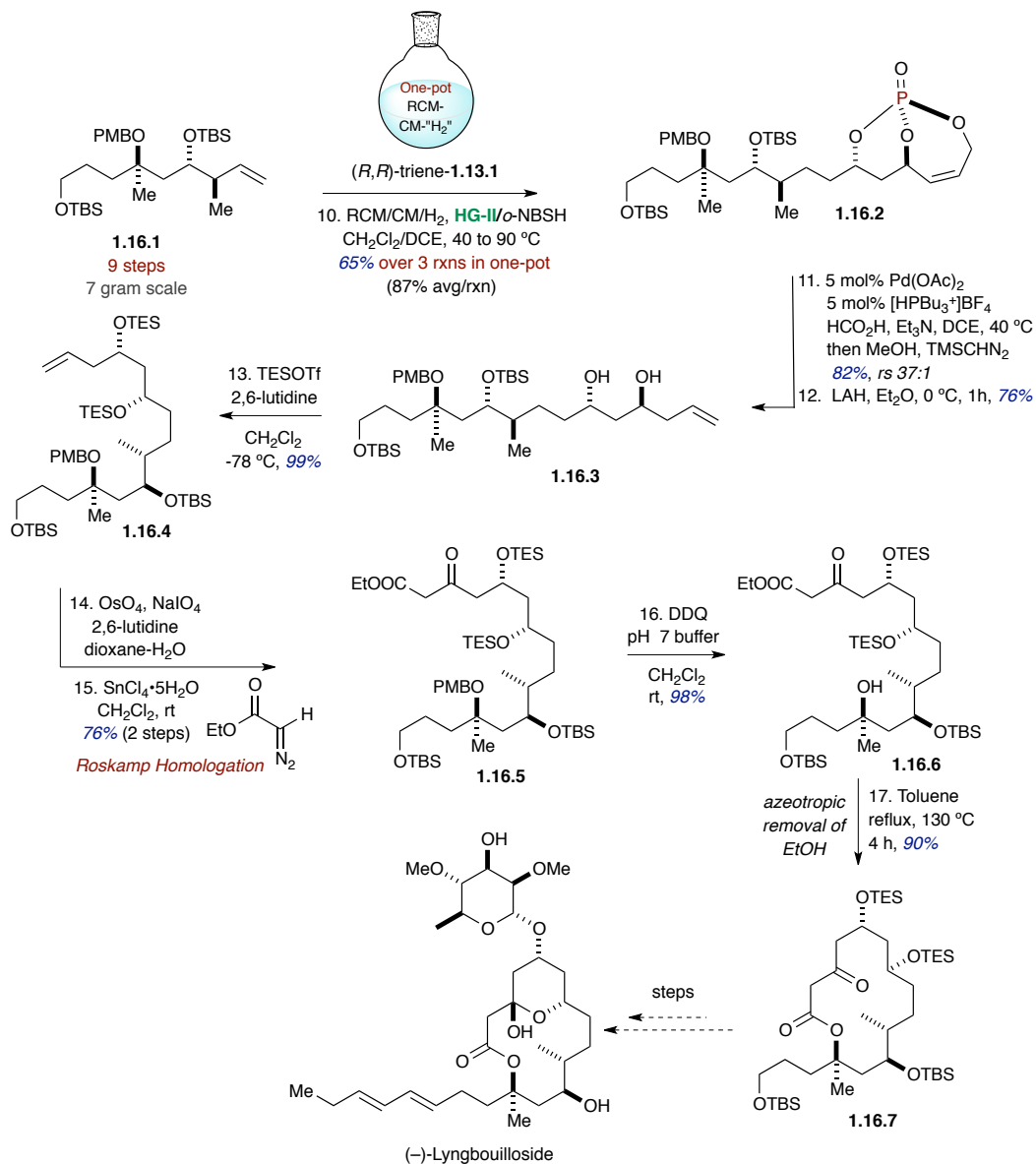
1.8.5. Synthesis of macrolactone core of lyngbouilloside

In 2015, Hanson and coworkers reported a concise synthetic pathway for the synthesis of the macrolactone core of the originally assigned structure of lyngbouilloside (Scheme 1.16).^{Error! Bookmark not defined.} The key reactions involved in the synthesis of macrolactone core **1.16.7** are one-pot sequential RCM/CM/“H₂”, Roskamp homologation, and Boeckman acylketene cyclization. Toward this goal, CM partner **1.16.1** was synthesized in 9 steps from commercially available geraniol. Next, the authors subjected the (*R,R*)-triene **1.13.1** and CM partner **1.16.1** to a phosphate tether-mediated one-pot sequential RCM/CM/“H₂” protocol to afford the bicyclic phosphate **1.16.2** in 65% yield over three reactions in one-pot.

With bicyclic phosphate **1.16.2** in hand, the authors performed Pd-catalyzed, reductive allylic transposition, followed by methylation of the resulting phosphoric acid, and reductive tether removal to afford the 1,3 *anti*-diol fragment **1.16.3** in 76% yield. The free alcohols of 1,3 *anti*-diol fragment **1.16.3** were silyl-protected using TESOTf and 2,6-lutidine to generate intermediate **1.16.4** in excellent yield. The terminal olefin in **1.16.4** was subjected to oxidative cleavage, employing the modified Johnson-Lemieux protocol developed by Jin and coworkers,⁴⁶ to afford the corresponding aldehyde. The crude aldehyde with out further purification was subjected to Roskamp homologation⁴⁷ to afford the β -keto ester **1.16.5** in 76% yield over two steps with only one purification procedure. PMB-deprotection of the tertiary alcohol in **1.16.5** afforded the cyclization

precursor **1.16.6** in 98% yield. The tertiary alcohol **1.16.6** was subjected to Boeckman acylketene cyclization conditions⁴⁸ to accomplish the synthesis of macrolactone core of lyngbouilloside in excellent yield. Further studies towards the completion of the molecule are underway.

Scheme 1.16. *Posphate tether-mediated synthesis of macrolactone core of (–)-lyngbouilloside.*



1.8.6. Synthesis of C9–C25 subunit of spirastrellolide B

In 2016, Hanson and coworkers reported an efficient synthesis of C9–C25 subunit **1.2e** of the marine natural product spirastrellolide B (Figure 1.3).^{Error! Bookmark not defined.} The key synthetic features include the union of the two key fragments **1.3a** and **1.3b** via a Suzuki-Miyaura coupling reaction. A late-stage one-pot deprotection/cascade Achmatowicz rearrangement–spiroketalization sequence to install the key spirocyclic intermediate present in the C9–C25 fragment of spirastrellolide B. The synthesis of the C9–C16 fragment **1.3b** was accomplished via a phosphate tether-mediated one-pot sequential RCM, a subsequent hydroboration-oxidation protocol, followed by stereoselective transformations in a facile manner. The spirocyclic intermediate was further functionalized by employing a Lindlar/NaBH₄ reduction protocol to accomplish the C9–C25 subunit **1.2e** of spirastrellolide B.

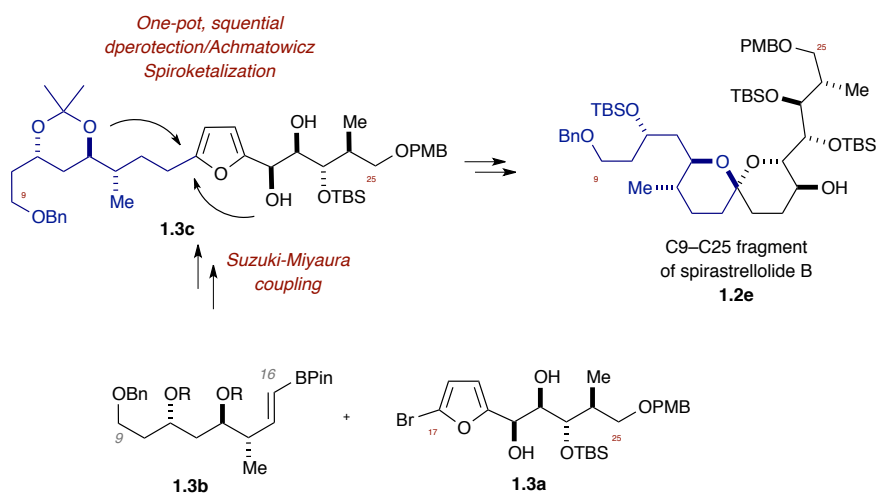


Figure 1.3. Retrosynthetic analysis of the C9–C25 subunit of spirastrellolide B.

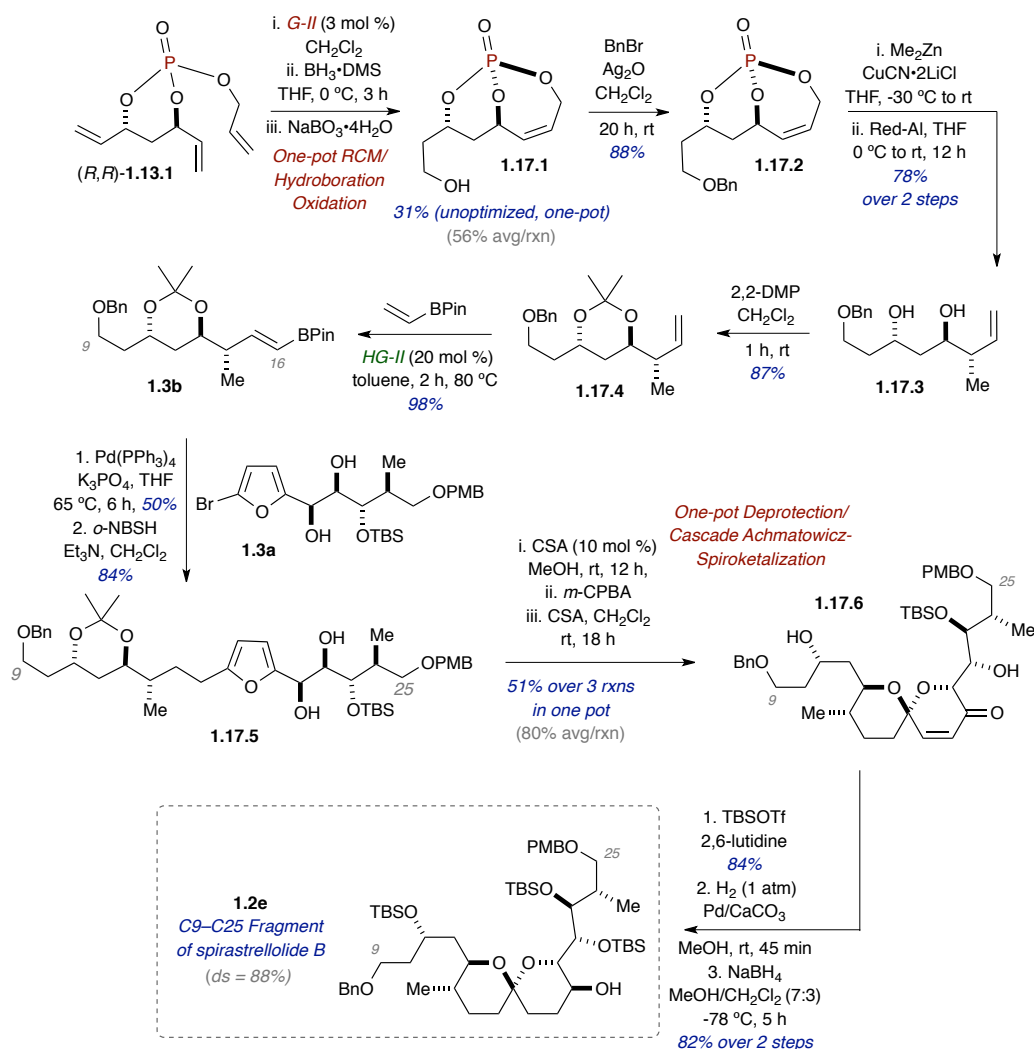
The forward synthesis of the C9–C25 subunit **1.2e** began with the synthesis of the C9–C16 polyol-containing fragment **1.3b** (Scheme 1.17), whereby, the triene phosphate (*R,R*)-**1.13.1** was subjected to a one-pot RCM/hydroboration oxidation sequence. In this

regard, the triene (*R,R*)-**1.13.1** was treated with **G-II** (3 mol%) and the resulting bicyclic phosphate was exposed to BH₃•DMS, followed by oxidation with sodium perborate to afford alcohol **1.17.1** in 31% yield over three reactions in one pot (56% average per reaction, not optimized). Subsequent benzyl protection of the primary alcohol with BnBr and Ag₂O afforded **1.17.2**. The bicyclic phosphate **1.17.2** was treated with *in-situ*-generated dimethyl cuprate, followed by reductive removal of the phosphate tether to provide diol **1.17.3** and install the C14-methyl group in regio- and diastereoselective fashion. Diol **1.17.3** was protected as an acetal to generate **1.17.4** in 87% yield, and subsequent cross metathesis of **1.17.4** with commercially available pinacol vinylboronate successfully furnished the intermediate **1.3b** in quantitative yield (98%).

The synthesis of C17–C25 fragment **1.3a** was accomplished in seven linear steps from commercially available (*S*)-Roche ester. With key fragments **1.3a** and **1.3b** in hand, a Suzuki-Miyaura coupling reaction of bromofuran **1.3a** with vinylboronate **1.3b** in the presence of Pd(PPh₃)₄ and K₃PO₄ furnished the coupling product in moderate yield (50%). Diimide reduction of the resulting olefinic bond using excess *o*-NBSH and Et₃N generated Achmatowicz-cyclization precursor **1.17.5** in 84% yield. With advanced intermediate **1.17.5** in hand, acetal deprotection using catalytic camphorsulfonic acid (CSA, 10 mol%), followed by cascade Achmatowicz-spiroketalization (*m*-CPBA, then CSA), furnished the required spiroketal-containing diol **1.17.6** in 51% yield over three reactions in one pot (80% av/rxn). Global TBS-protection with TBSOTf and 2,6-lutidine, followed by C–C double bond reduction with H₂ and Lindlar catalyst furnished the ketone. Diastereoselective reduction (ds = 88%) of the resultant ketone with NaBH₄, afforded the C9–C25 fragment of spirastrellolide B (**1.2b**) in 82% yield over two

reactions.

Scheme 1.17. Efficient synthesis of C9–C25 fragment of spirastrellolide B.

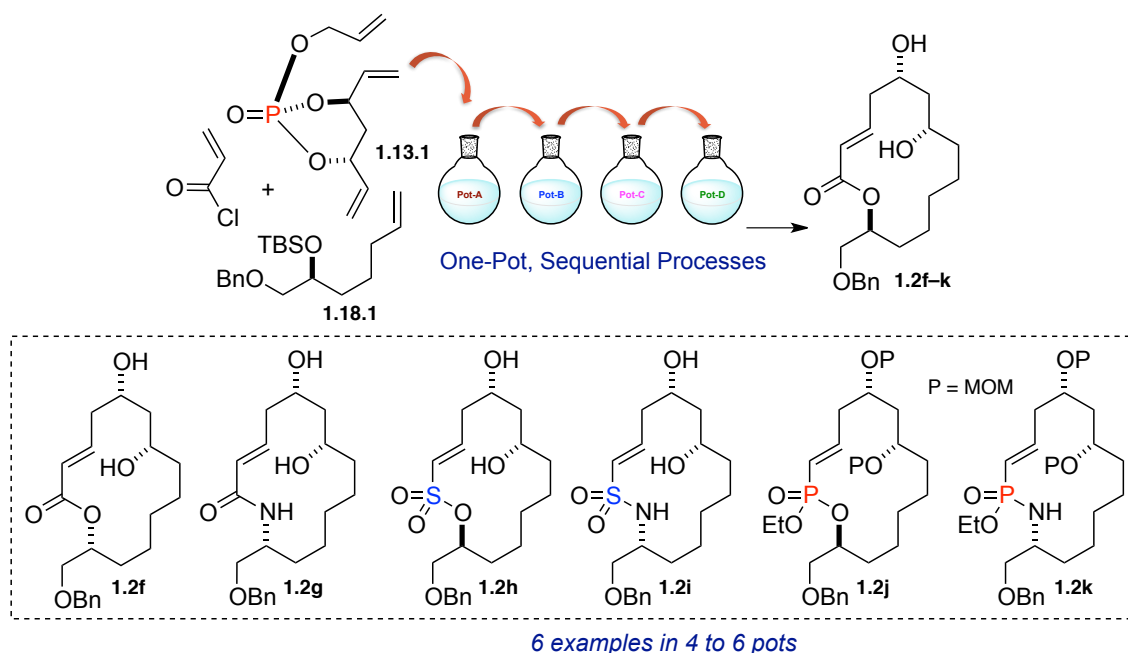


1.8.7. Synthesis of α,β -unsaturated macrocycles via consecutive 4-to-6, one-pot sequential operations (Chapter 2)

Chapter 2 of this dissertation describes a concise synthesis of novel macrocycles possessing α,β -unsaturated chemotypes that employ a series of one-pot sequential protocols (Scheme 1.18).²⁶ This efficient and library amenable approach utilizes four to six consecutive one-pot sequential processes, highlighting phosphate tether-mediated asymmetric syntheses of novel carbon-, sulfur- and phosphorus-based macrocycles **1.2f**–

k in good to excellent yields from readily prepared (*R,R*)-triene **1.13.1** and CM partner **1.18.1**.⁴⁹ A notable merit of the method is the application of multiple consecutive pot-economical operations that significantly avoid workup and purification procedures between successive reactions, reducing operational time and waste generation. The synthesis of these structurally diverse α,β -unsaturated macrocycles will be discussed in detail in chapter-2 of this dissertation.

Scheme 1.18. Syntheses of α,β -unsaturated macrocycles via a sequence of four-to-six one-pot sequential processes.

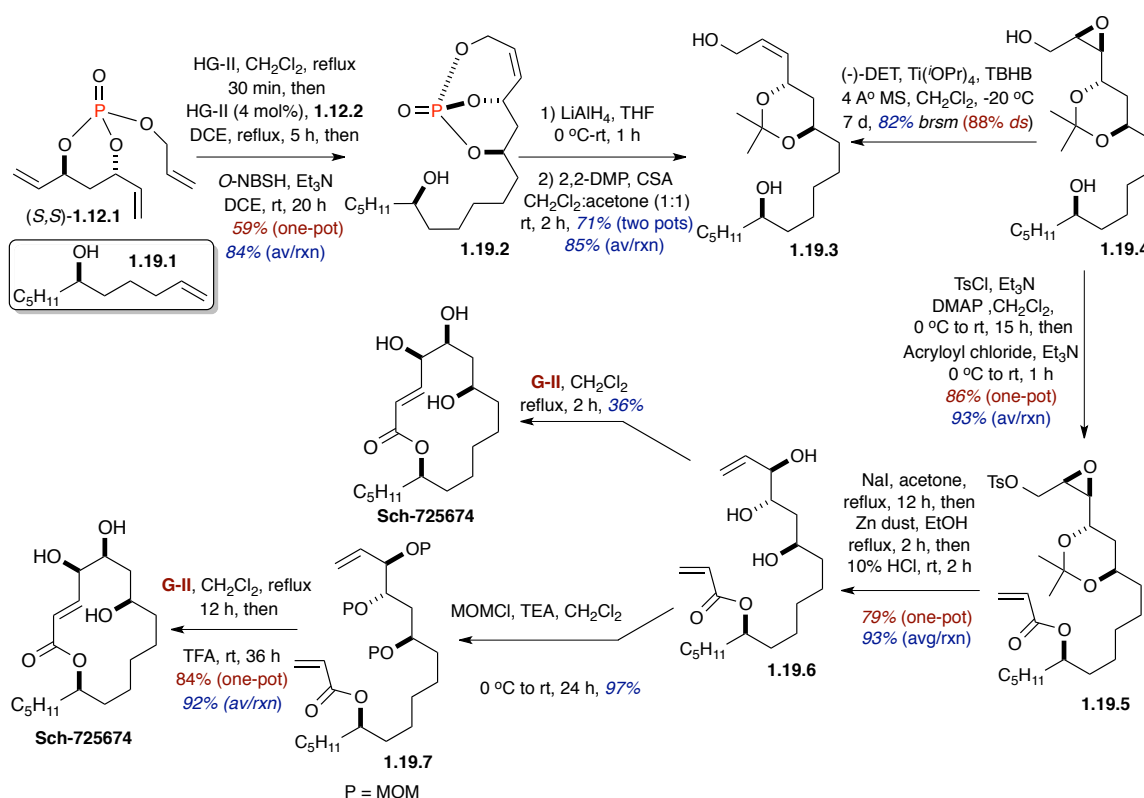


1.8.8. Pot-economical approach for the total synthesis of Sch-725674 and corresponding analogs (Chapter 3)

Chapter 3 of this dissertation describes a pot economical approach for the asymmetric synthesis of antifungal natural product Sch-725674 (Scheme 1.19).²⁵ The key structural features of this natural product include a 14-membered ring, an *E*-configured α,β -unsaturated ester, a lipophilic *n*-pentyl side chain, and a 1,3-*anti*-diol moiety embedded within a four-carbon subunit containing three stereogenic carbinol centers.

This approach takes the advantage of a number of one-pot sequential transformations including one-pot sequential RCM/CM/“H₂” protocol, a one-pot tosylation/acrylation sequence, a one-pot sequential Finkelstein reaction/Boord olefination/acetonide-deprotection, and final RCM/MOM-deprotection sequence. These one-pot sequential operations streamlined the synthesis route by reducing isolation and purification procedures, thus saving time. Overall, an asymmetric route has been developed that was efficiently accomplished to synthesize Sch-725674 in seven pots from phosphate (*S,S*)-triene **1.12.1** and CM partner **1.19.1** with minimal purification procedures.

Scheme 1.19. Pot-economical, asymmetric syntheses of Sch-725674.



We anticipated that the outlined pot-economical and library amenable approach for the synthesis of Sch-725674 can be further exploited for the synthesis of a diverse range of sterically, electronically and stereo-chemically attenuated analogs (**1.2l–p**) of

Sch-725674 (Figure 1.4). The key reactions involved in the synthesis of Sch-725674 analogs (**1.2l–p**) were one-pot sequential RCM/CM/“H₂”, regio- and diastereoselective cuprate addition, one-pot sequential protecting group manipulation, one-pot sequential Mitsunobu/reduction/acrylation and a final RCM/deprotection sequence. Employing these one-pot sequential protocols, we were able to accomplish the synthesis of five structurally diverse analogs (**1.2l–p**) in a rapid, efficient, and pot-economical manner with amine, alcohol and α,β -unsaturated lactone/lactam functionality incorporated in them. All five Sch-analogs have been submitted for antifungal and antibacterial screening to our collaborators.

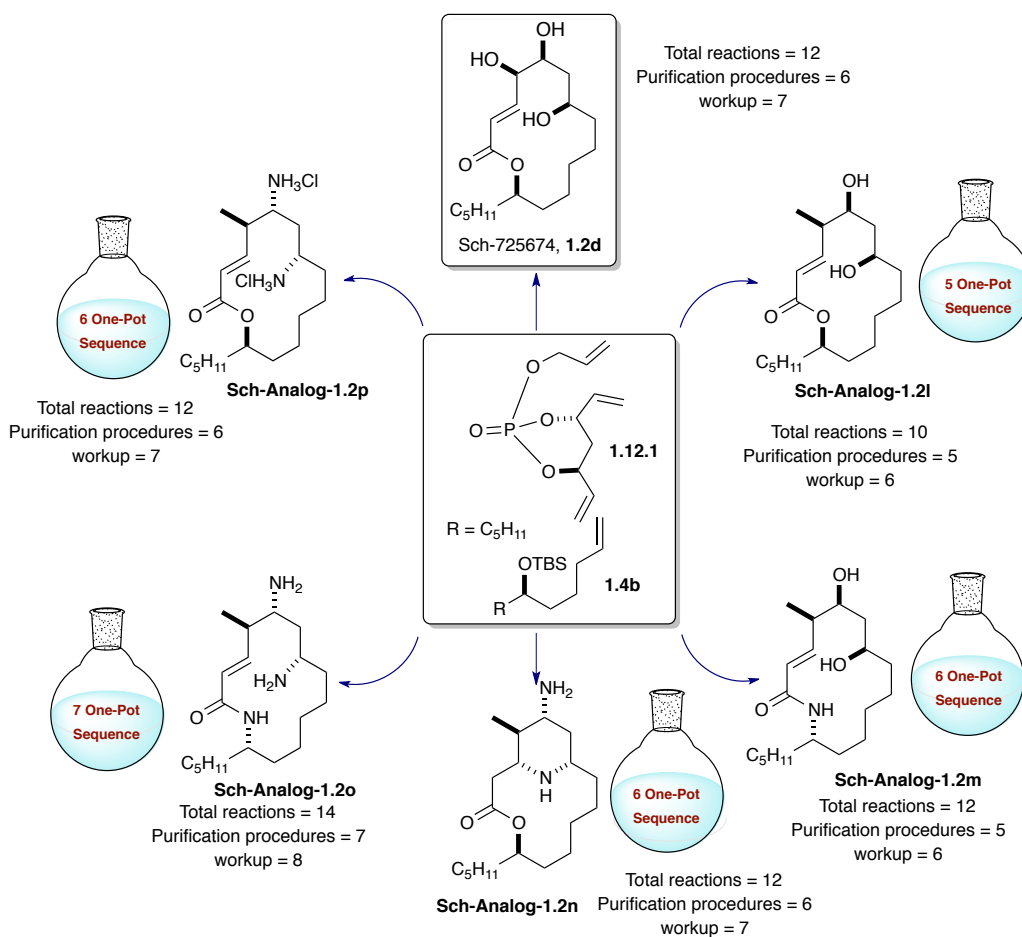
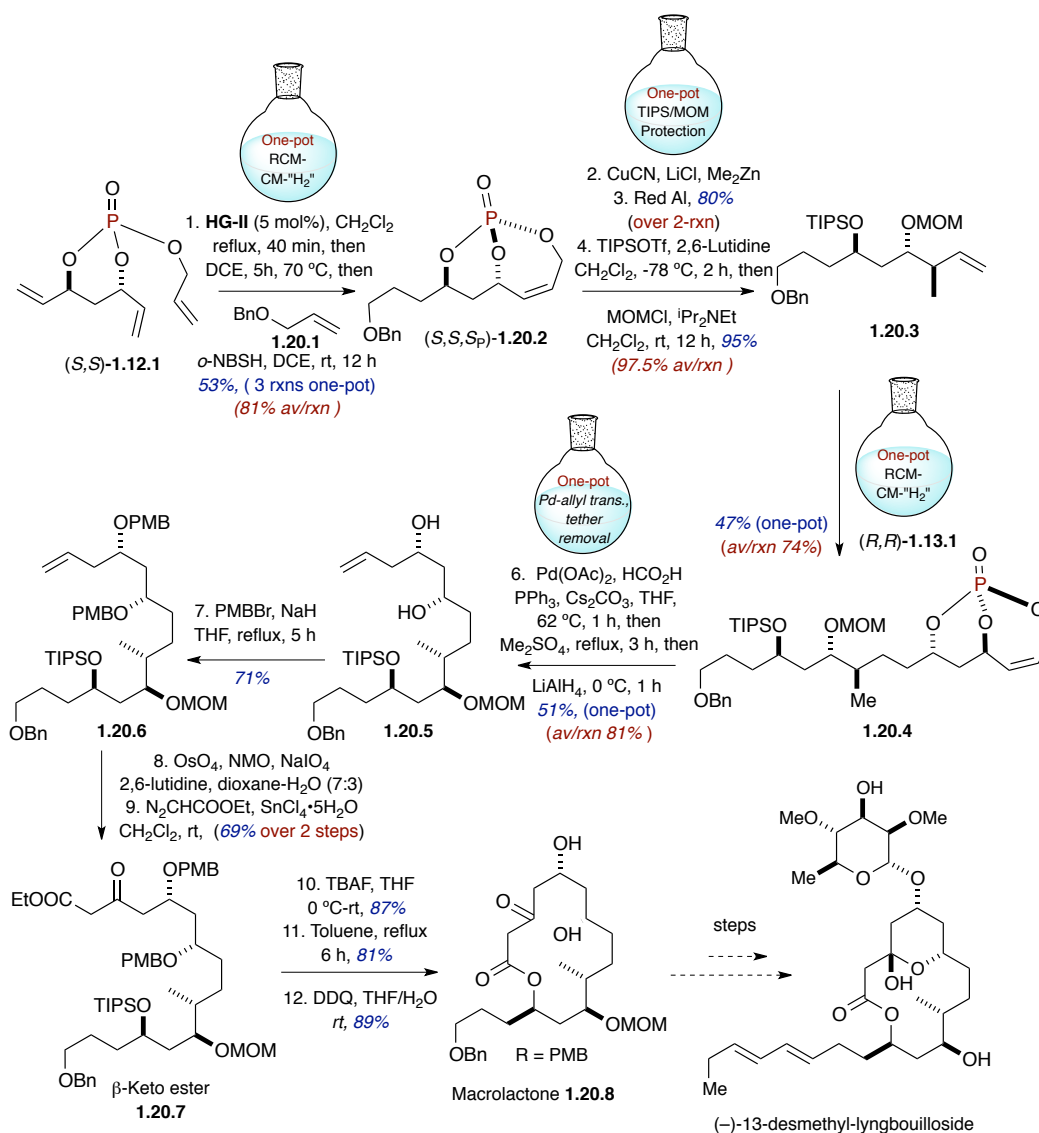


Figure 1.4. Antifungal natural product Sch-725674, **1.2d** and derivatives **1.2l–p**.

1.8.9. Synthetic studies toward the total synthesis of (–)-13-desmethyl-lyngbouilloside (Chapter 4)

Chapter 4 of this dissertation describes the asymmetric total synthesis of (–)-13-desmethyl-lyngbouilloside, an unnatural analog of lyngbouilloside (Scheme 1.20). The forward synthesis of (–)-13-desmethyl-lyngbouilloside commenced with phosphate tether-mediated one-pot sequential RCM/CM/ chemoselective hydrogenation to couple (*S,S*)-triene **1.12.1** and CM **1.20.1**, followed by regio- and diastereoselective cuprate addition to the resulting bicyclic phosphate **1.20.2**. The resulting 1,3-*anti* diol was subjected to a one-pot regioselective TIPS-protection, followed by MOM-protection, to afford the stereotriad-bearing subunit **1.20.3**. With CM partner **1.20.3** in hand, efforts were focused on coupling with (*R,R*)-trien **1.13.1** via an iterative use of one-pot sequential RCM/CM/chemoselective hydrogenation, followed by tether removal via Pd-catalyzed reductive allylic transposition, to furnish the advance fragment **1.20.5**. The free alcohols in 1,3-*anti* diol fragment **1.20.5** were protected as benzyl ethers, followed by oxidative cleavage of the terminal olefin in **1.20.6** and Roskamp homologation, to afford the β -ketoester **1.20.7**. TIPS-deprotection using TBAF, followed by Boeckman acylketene cyclization to furnish the fully functionalized macrolactone core of (–)-13-desmethyl-lyngbouilloside. Further studies towards the completion of the molecules are underway.

Scheme 1.20. Asymmetric total synthesis of (–)-13-desmethyl-lyngbouilloside



1.9. Conclusion

In summary, one-pot sequential operations are efficient methods for carrying out several bond transformations and stereocenter formations in a single reaction vessel, which minimize workup and purification procedures in multistep synthesis to reduce chemical waste generation and to save time. Moreover, one-pot sequential protocols are not only a useful synthetic method to be adopted for the production of target molecules,

but also represent a promising green approach in modern-day organic synthesis. Therefore, carefully designed, one-pot sequential reaction protocols are important in streamlining the synthesis of target medicinal compounds, bioactive natural products, and their corresponding analogs.

1.10. Special Acknowledgment

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(a) Javed, S.; Bodugam, M.; Ganguly, A.; Torres, J.; Hanson, P. R. Modular Synthesis of Novel Macrocycles Bearing α,β -Unsaturated Chemotypes via a Series of One-Pot, Sequential Protocols. *Chem. Eur. J.* **2016**, *22*, 6755–6758. (b) Bodugam, M.; Javed, S.; Ganguly, A.; Torres, J.; Hanson, P. R. A Pot-Economical Approach to the Total Synthesis of Sch-725674. *Org. Lett.* **2016**, *18*, 516–519. (c) Maitra, S.; Bodugam, M.; Javed, S. Hanson, P. R. Efficient Synthesis of the C9–C25 Subunit of Spirastrellolide B. *Org. Lett.* **2016**, *18*, 3094–3097.

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Chapter 2

Modular Synthesis of Novel Macrocycles Bearing α,β -Unsaturated Chemotypes
via a Series of One-pot Sequential Processes.

2.1. Introduction

The development of efficient, pot- and step-economical protocols for the synthesis of medium- and large-sized bioactive heterocycles¹ is important in the screening campaigns for facilitating drug discovery.² In particular, naturally occurring macrocyclic lactones, lactams, and their synthetic analogs represent an important class of bioactive molecules in compound collections.^{1,3} Additionally, macrocycles are privileged structures for biological studies as they can display unique features, such as conformational pre-organization, flexibility, selectivity, and potentially higher affinity with protein targets.⁴ Hence, macrocycles are promising molecules for the modulation of challenging processes,⁵ such as protein-protein interactions⁶ and epigenetic events.⁷ Macrocycles, both naturally occurring and synthetic analogs, display a broad spectrum of biological activities in a variety of different areas ranging from anti-fungal activity,⁸ anthelmintic activity,⁹ hepatitis C virus (HCV), NS3/4A serine protease,¹⁰ antibiotics,¹¹ CDK2/cyclin A inhibitors,¹² Hsp90 inhibitors,¹³ protein kinase C (PKC) inhibitors,¹⁴ in drug discovery¹⁵ to insecticidal agents in agriculture.¹⁶ Furthermore, the significance of macrocycles has been demonstrated in drug development with more than a hundred naturally occurring and synthetic macrocycle-containing compounds currently being explored in therapy.¹⁷

Of particular interest, naturally occurring macrocycles bearing α,β -unsaturated entities have shown a wide range of important medicinal activities, including antifungal, anticancer, and antibacterial (Figure 2.1).¹⁸ Notably, a number have been found to covalently react with proteins to carry out their biological role.^{19,20} Examples include

protein kinase inhibitor hypothemycin^{19a} and antibacterial agent *atrop*-abyssomicin C,²⁰ which function by covalently binding to their targets through Michael addition of a cysteine residue.

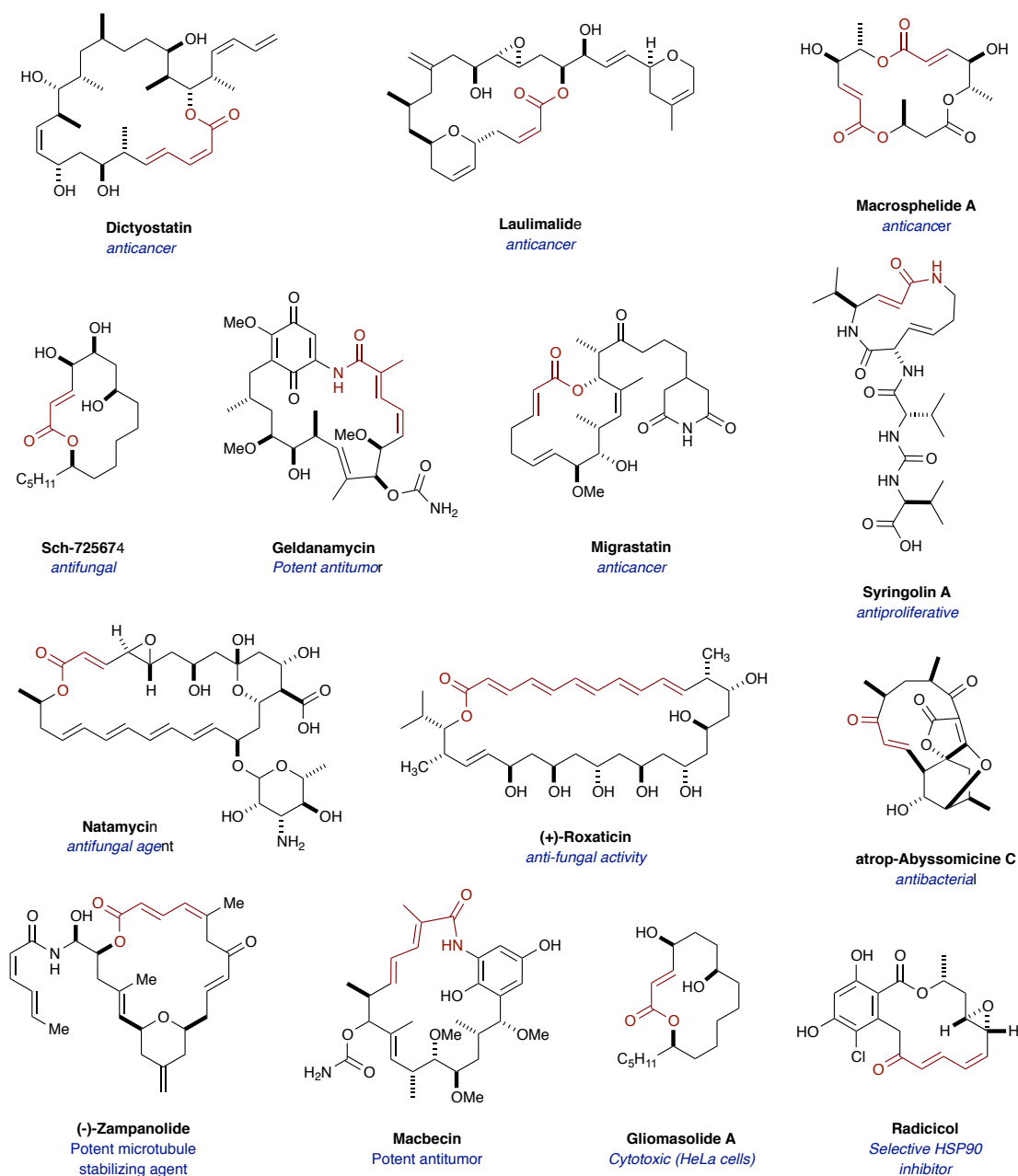


Figure 2.1. Bioactive macrocyclic natural products bearing α,β -unsaturated chemotypes.

Similarly, syringolin A targets the proteasome via irreversible reaction²¹ of a catalytic threonine at the α,β -unsaturated amide.^{19c} As a result of these contributions and others, scaffolds bearing electrophilic functionalities are highly attractive biological probes for applications in imaging,²² activity-based protein profiling,²³ and therapeutics.^{24,2d-e}

2.2. Previous strategies for the syntheses of medium to large-size heterocycles

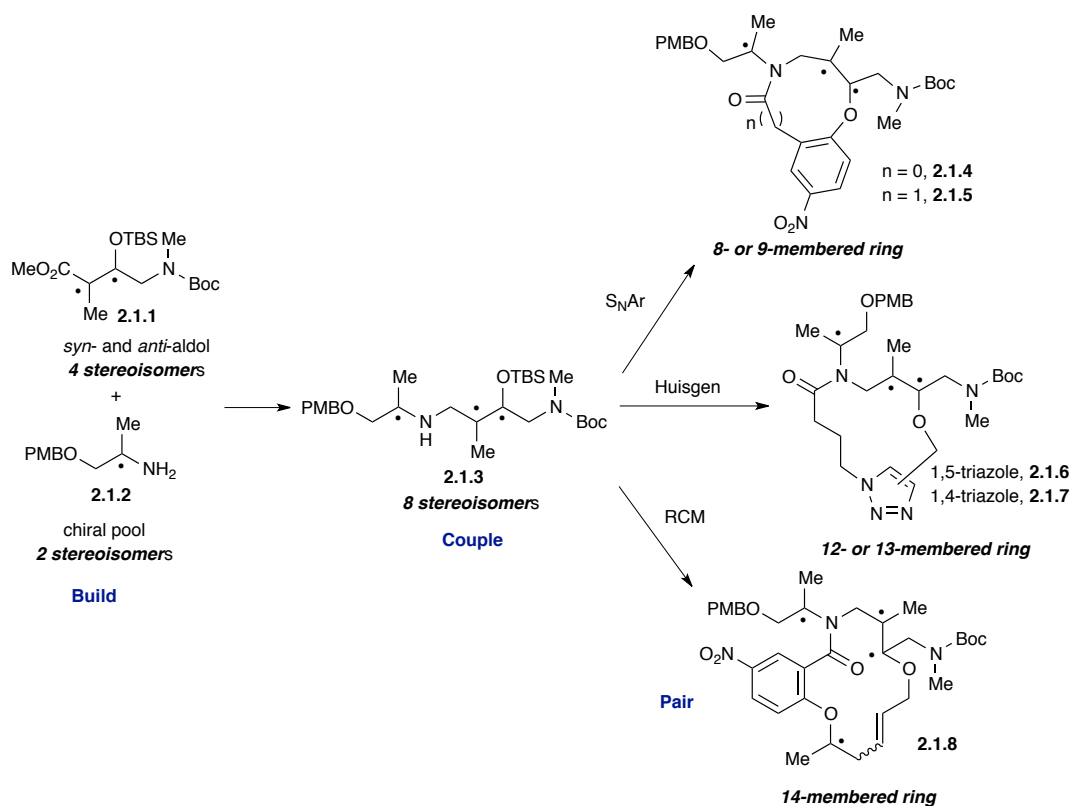
As evident from their biological activities (Figure 2.1), macrocycles are key structural elements in the synthesis of bioactive natural products and natural product-based libraries for probe development and drug discovery.^{25,5a} However, macrocycles are severely underexplored due to their structural complexity and synthetic intractability. Furthermore, it is assumed that natural product macrocycles and their synthetic analogs will tend to violate the recommended ranges in Lipinski's rule-of-five and other guidelines for balancing aqueous solubility and lipid-membrane permeability to achieve oral absorption.²⁶ However, this is not the case for many bioactive natural macrocyclic agents (erythromycin, rapamycin, vancomycin, cyclosporin) and their synthetic analogs, which serve as drugs and drug candidates in the early phase clinical development.²⁷ These challenges associated with the molecular structure and synthesis limit the pharmaceutical application of macrocycles in probe development and drug discovery. In spite of these challenges, and motivated by the intriguing biological activity and inspired by synthetic complexity of naturally occurring macrocycles,^{2b,17a} substantial efforts have been devoted toward highly efficient and robust synthetic methods for the preparation of macrocycles. Over the last decade, significant efforts have been undertaken toward the synthesis of complex naturally-occurring macrocycles and their

synthetic derivatives. A number of different synthetic protocols have been developed for the synthesis of a diverse range of macrocycles.¹ The focus of this section will be on the recent synthetic methodologies reported in literature for the synthesis of macrocyclic compounds, which are the integral parts of bioactive natural products and drug-like molecules.

2.2.1. Synthesis of medium- and large-sized rings via Build/Couple/Pair (B/C/P) strategy

In 2010, the Marcaurelle group reported an aldol-based build/couple/pair (B/C/P) strategy for the syntheses of stereochemically and skeletally diverse collection of medium- to large-sized rings (Scheme 2.1).²⁸ In the *build* phase, four stereoisomers of Boc-protected γ -amino acid **2.1.1** were generated through asymmetric *syn*- and *anti*-aldol reactions. Additionally, PMB-protected D- and L-alaninol **2.1.2** were synthesized, which served as coupling partners. In the *couple* phase, a coupling reaction of aldol-derived amino acid **2.1.1** and chiral amine **2.1.2** afforded eight stereoisomers of the corresponding amide, which were subsequently reduced to amines **2.1.3**. In the *pair* phase, the linear amines **2.1.3** were cyclized via three different ring forming strategies; nucleophilic aromatic substitution (S_NAr), Huisgen [3+2] cycloaddition and/or ring-closing metathesis to furnish structurally diverse collection of 8- to 14-membered scaffolds **2.1.4–2.1.8**. The compounds generated through this B/C/P strategy were screened, which led to the discovery of potent macrocyclic histone deacetylase inhibitors.

Scheme 2.1. Aldol-based B/C/P strategy for the syntheses of structurally diverse macrocycles.

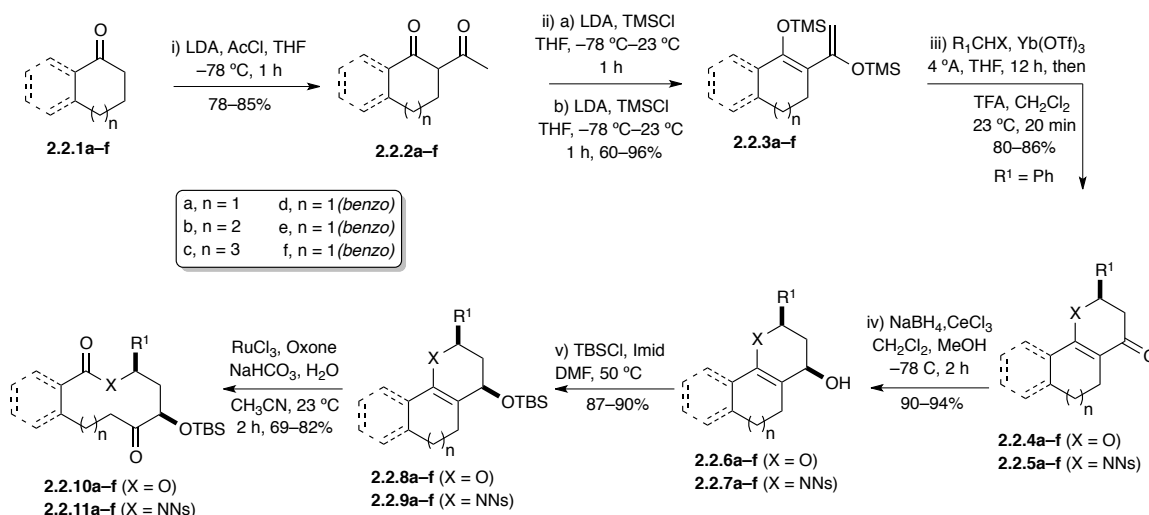


2.2.2. Synthesis of macrolactones and macrolactams via oxidative ring expansion strategy

In 2012, Tan and co-workers reported a modular and concise approach for the diversity-oriented synthesis of functionalized macrolactone and macrolactam scaffolds via oxidative cleavage of the bridging double bond in polycyclic enol ethers and enamines (Scheme 2.2).²⁹ The requisite polycyclic enol ethers and enamine scaffolds, bearing different functional handles, were assembled in four to five synthetic transformations. β -keto esters **2.2.2a-f** were generated via α -C acylation of cyclic ketone **2.2.1a-f** using lithium diisopropylamide (LDA).³⁰ The resulting cyclic ketones were

subsequently treated with two equivalents of LDA and TMSCl sequentially to provide the dienes **2.2.3a-f**. Hetero-Diels-Alder reaction of diene **2.2.3a-f** with aldehyde and *N*-nosyl imine furnished dihydropyrones **2.2.4a-f** and dihydropyridones **2.2.5a-f** in good yield (90–94%), respectively.³¹ Diastereoselective reduction of the ketone functionality in **2.2.4a-f** and **2.2.5a-f** using NaBH₄ and CeCl₃, followed by TBS-protection afforded the corresponding ring expansion precursors **2.2.8a-f** and **2.2.9a-f** in good to excellent overall yields.

Scheme 2.2. Diversity-oriented syntheses of macrolactones and macrolactams via oxidative ring expansion approach.



After screening a variety of different reaction conditions for oxidative ring expansion, polycyclic enol ethers **2.2.8a-f** and enamine **2.2.9a-f** were successfully transformed to macrolactone and macrolactam scaffolds in moderate to good yields utilizing catalytic RuCl₃ and stoichiometric amounts of additives (oxone). The resulting macrocycles were subjected to a detailed cheminformatic analysis, which showed that

these structurally diverse macrolactones and macrolactams overlap with the chemical space of bioactive natural products, high-profile synthetic drugs, and drugs-like libraries that are currently targeted by the pharmaceutical industry.

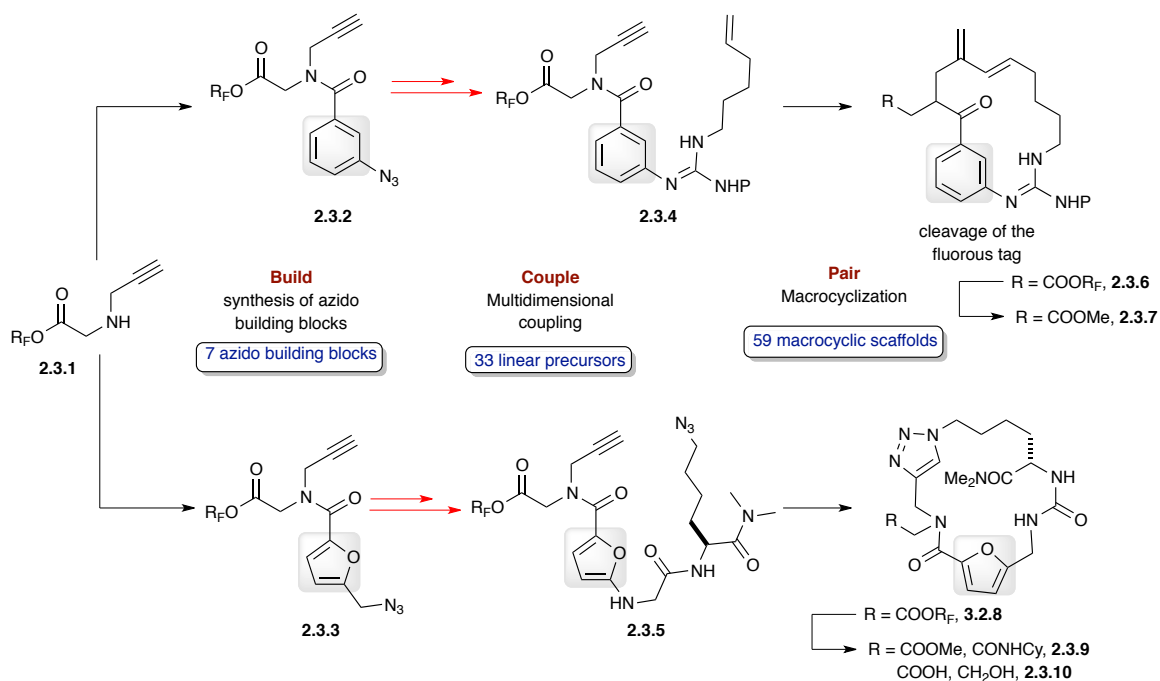
2.2.3. A diversity-oriented synthesis of functionalized macrocyclic scaffolds via multidimensional coupling strategy

In 2013, the Spring group reported an advanced diversity-oriented strategy, which involved multidimensional coupling reactions for the syntheses of functionalized macrocyclic scaffolds from simple and easily prepared starting materials (Scheme 2.3).³² This strategy involved exploiting the pluripotent reactivity of aza-ylides derived from readily prepared azides. Seven azido building blocks were readily generated in the *build phase* from common precursors **2.3.1**. The azides **2.3.2** and **2.3.3** were converted *in situ* to aza-ylides, which were subsequently treated with a variety of electrophiles in the multidimensional *coupling phase* through an aza-Wittig reaction to generate various structural motifs **2.3.4** and **2.3.5**. The aza-Wittig reaction installed the terminal azide or alkyne functionality, which served as a macrocyclization handle in the subsequent *pair* phase.

The macrocyclization was accomplished either via enyne metathesis³³ or copper- and ruthenium-catalyzed³⁴ azide alkyne cycloaddition to afford structurally diverse macrocyclic compounds **2.3.6–2.3.10**. The resulting compounds were subsequently subjected to fluorine-tag cleavage to provide the final macrocyclic scaffolds. This efficient and divergent macrocyclization strategy enabled the synthesis of 73 compounds based on 59 discrete scaffolds in only four to five steps. The polyfluorocarbon-tag was utilized to facilitate the purification procedures. The principal moment-of-inertia³⁵ plot

indicated that the diverse functionalized macrocyclic scaffolds, prepared through this advanced diversity-oriented strategy, cover a broad range of molecular shapes.³²

Scheme 2.3. Diversity-oriented synthesis of a macrocyclic scaffolds via a multidimensional coupling strategy.

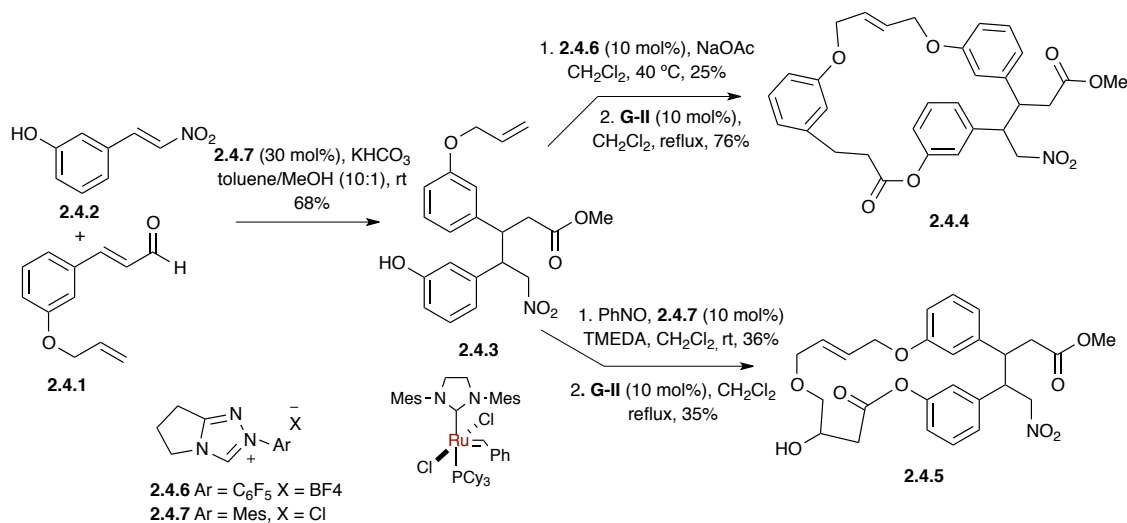


2.2.4. Organo- and metal-catalyzed synthesis of drug-like macrocyclic scaffolds

In 2014, Spring and co-workers developed an orthogonal organo- and metal-catalyzed strategy towards the diversity-oriented synthesis of natural product-like macrolactones by exploiting the pluripotency of aldehyde (Scheme 4).³⁶ Aldehyde **2.4.1** and its coupling partner **2.4.2** were readily prepared in a few steps from commercially available starting materials. Aldehyde **2.4.1** was treated with the coupling partner **2.4.2** utilizing NHC-catalyst (**2.4.6** and **2.4.7**) to generate intermediate **2.4.3** in good yield. After the first coupling event, the side chain in intermediate **2.4.3** was further extended

using a build/couple/couple (B/C/C) sequence. Finally, the macrocyclization of linear precursors was achieved via RCM reaction using **G-II** catalyst in moderate to good yields.

Scheme 2.4. Synthesis of drug-like macrolactone utilizing B/C/C/P strategy.

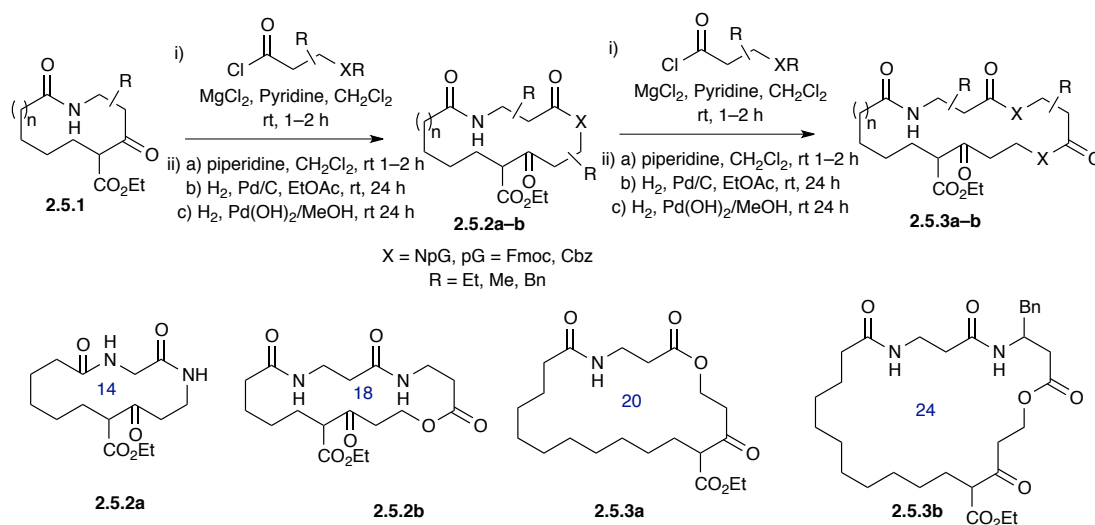


2.2.5. Synthesis of diverse medium to large-macrocycles via Successive Ring Expansion (SuRE) strategy

In 2015, Unsworth and co-workers reported the synthesis of structurally diverse, functionalized medium to large-macrocycles utilizing a Successive Ring Expansion (SuRE) approach (Scheme 2.5).³⁷ This method was established via a one-pot acylation/ring-expansion sequence, in which the linear fragments were inserted sequentially into a cyclic β -ketoester moiety **2.5.1**. The products **2.5.1** underwent ring expansion to generate medium to large macrocycles **2.5.2a–b**. This coupling/ring expansion sequence can be repeated multiple times to generate functionalized macrocyclic compounds of any size **2.5.3a–b**. The benefits of the SuRE strategy include i) the generation of diverse families of functionalized macrocycles, ii) freedom to install a

variety of different functional groups to macrocycles, iii) there is no need to perform a discrete end-to-end macrocyclization step, which needs high dilution.

Scheme 2.5. *Synthesis of medium to large macrocycles via successive ring expansion strategy.*



2.3. Results and Discussions

Motivated by the biological activities and electrophilic nature of α,β -unsaturated macrolactone- and macrolactam-containing bioactive natural products and medicinal drugs (Figure 2.1), we are interested in the syntheses of both cyclic and acyclic α,β -unsaturated chemotypes (Figure 2.2). In particular, the synthesis of electrophilic motifs, with exocyclic α,β -unsaturated ketones or amide functionality attached to a ring. Representative examples, include: (i) azinomycin containing an exocyclic α,β -unsaturated ketones or amide functionality attached to a ring (**2.2a**, potent anti-tumor), (ii) parthenolide (**2.2b**) containing an exocyclic enone and possessing anti-inflammatory activity, (iii) systems possessing acyclic α,β -unsaturated functionalities **2.2c** (a number of

cysteine protease inhibitors), (iv) Sch-725674 (**2.2d**) an α,β -unsaturated macrolactone possessing antifungal activity,³⁸ and (v) macbecin (**2.2d**), a macrolactam with a dienyl moiety incorporated in the macrocyclic ring possessing potent antitumor activity (Figure 2.2).³⁹ Furthermore, we anticipated that these electrophilic motifs once synthesized could be attenuated electronically, sterically, stereochemically, and lipophilically, as well as by potentially masking their α,β -unsaturated functionality.

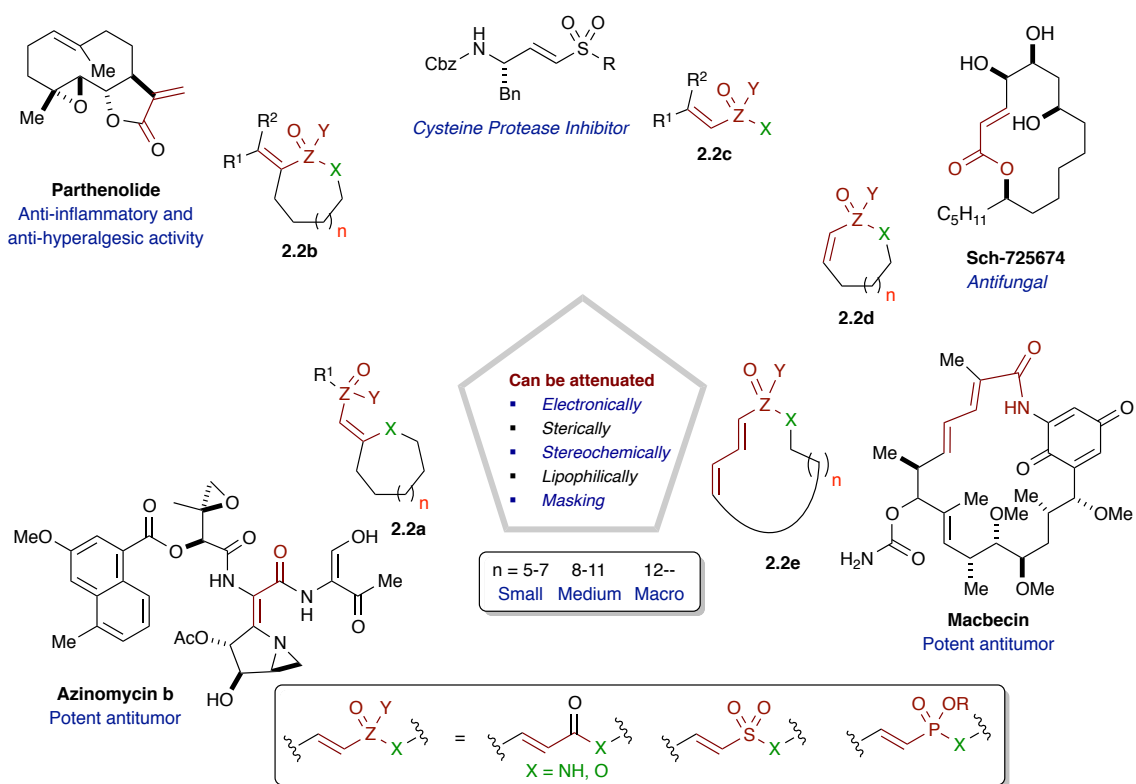


Figure 2.2. α,β -unsaturated chemotypes: reactive electrophiles

2.3.1. Rational design

At the outset of our studies, we investigated the preparation of 14-membered macrolactone **2.3a** via a sequence of four consecutive one-pot processes to significantly reduce compound isolations and chromatographic purifications to achieve concise and rapid synthesis (Figure 2.3). The strategy highlights the utilization of a phosphate tether-mediated one-pot sequential RCM/CM/chemoselective hydrogenation [“H₂”] protocol⁴⁰ applied to the phosphate triene (*R,R*)-**2.3g**⁴¹ and cross-metathesis (CM) partner **2.3h**,⁴² followed by a one-pot sequential Pd-catalyzed allylic transposition and tether removal pathway. The method continues with subsequent simple protecting group manipulations that are also streamlined in a one-pot process. The synthesis of **2.3a** was accomplished in short order via a final one-pot protocol that consists of a ring-closing metathesis (RCM) and MOM deprotection sequence. Overall, the synthesis of macrolactone **2.3a** entails the use of a series of four consecutive, one-pot sequential operations starting from phosphate (*R,R*)-**2.3g**.

To assess the library amenability of the method, we envisioned diversifying the macrocyclic α,β -unsaturated unit via installation of electronically attenuated electrophilic warheads. This was accomplished at the alcohol functionalization stage, following the MOM-protection and TBS-deprotection, by introducing sulfonylation or phosphorylation reactions in addition to acrylation (Figure 2.3), which provided the macrosultone **2.3b** and macrophostone **2.3c** analogs. Diversification at the electrophilic warhead was further applied via a one-pot sequential Mitsunobu reaction, azide reduction and amine functionalization protocol to construct macrolactam surrogates (Path-B, Figure 2.3),

including sulfur and phosphorous-based α,β -unsaturated chemotypes (**2.3d–f**).

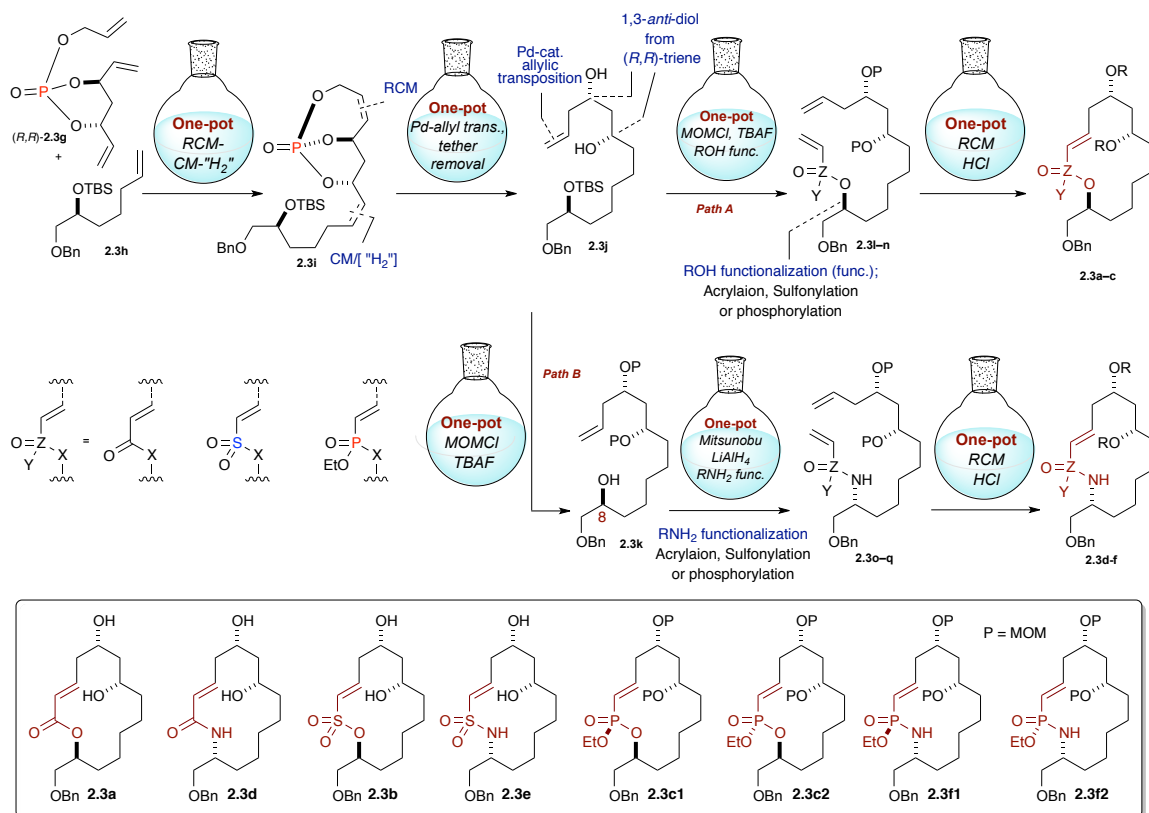


Figure 2.3. Syntheses of α,β -unsaturated macrocycles via a sequence of four to six one-pot sequential processes.

2.3.2. Synthesis of 14-membered macrolactone **2.3a** and macrosulfone **2.3b**

Initial attempts were focused on the synthesis of 14-membered macrolactone **2.3a** and macrosulfone **2.3b** starting from (R,R) -triene-**2.3g** and CM partner **2.3h** via a series of four consecutive one-pot sequential operations. The key reactions involved in the generation of macrolactone and macrosulfone are (i) a phosphate tether-mediated one-pot sequential RCM/CM/chemoselective hydrogenation ["H₂"] protocol,⁴⁰ (ii) one-pot sequential Pd-catalyzed reductive allylic transposition/methylation/phosphate tether

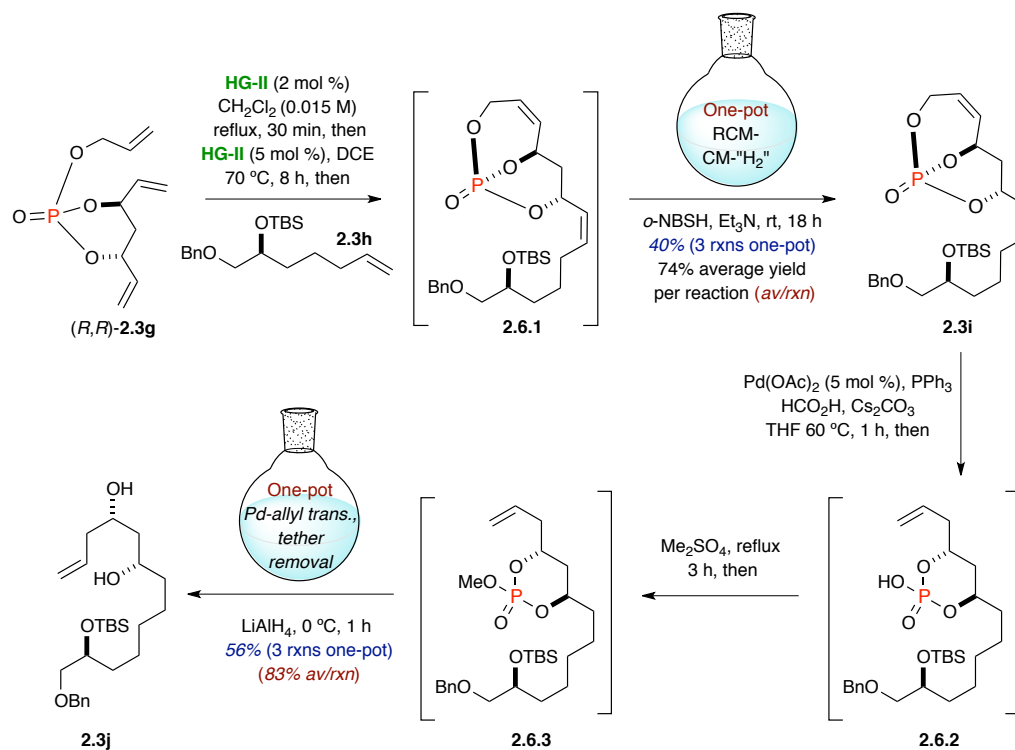
removal,⁴³ (iii) one-pot MOM-protection/TBS-deprotection/acrylation or sulfonylation and (v) a final one-pot RCM/MOM-deprotection protocol. Overall, the synthesis of the 14-membered macrocycles (macrolactone and macrosultone) were accomplished in a sequence of four consecutive pots, consisting of 11 reactions, and starting from readily-prepared triene (*R,R*)-**2.3g** and CM partner **2.3h** with only four workup and purification procedures.

Efforts towards the synthesis of macrolactone **2.3a** commenced with our previously developed phosphate tether-mediated one-pot sequential RCM/CM/chemoselective hydrogenation [H_2] protocol to couple phosphate triene (*R,R*)-**2.3g** and CM partner **2.3h**,⁴² providing bicyclic phosphate **2.3i** (Scheme 2.6). (*R,R*)-triene **2.3g** was first subjected to RCM reaction in the presence of the Hoveyda-Grubbs II (**HG-II**) catalyst⁴⁴ in refluxing CH_2Cl_2 . After completion of RCM reaction, the solvent was evaporated under reduced pressure and CM partner **2.3h** in dichloroethane (DCE) was added to the crude reaction mixture, followed by addition of the **HG-II** catalyst under argon. After completion of the CM reaction, subsequent chemoselective diimide reduction of CM adduct **2.6.1** with *o*-nitrobenzenesulfonyl hydrazine (*o*-NBSH)⁴⁵ and Et_3N (2g/mL of *o*-NBSH) in CH_2Cl_2 at room temperature, furnished bicyclo[5.3.1]phosphate **2.3i**. This first one-pot operation afforded phosphate triester **2.3i** in 40% overall yield over the course of three reactions, representing an average yield of 74% for each reaction in the same flask (74% av/rxn).

Exploiting the orthogonal leaving and protecting group ability of bicyclic phosphate **2.3i**, we next applied a one-pot sequential Pd-catalyzed, reductive allylic

transposition/methylation/phosphate tether removal protocol.⁴³ In this regard, the bicyclic phosphate **2.3i** was subjected to Pd-catalyzed, reductive allylic transposition [$\text{Pd}(\text{OAc})_2$, PPh_3 , HCOOH , Cs_2CO_3], and subsequent methylation utilizing dimethyl sulphate ($(\text{MeO})_2\text{SO}_2$) to generate the phosphate triester **2.6.3**. Next, in the same pot, the crude phosphate triester, without further purification and solvent change, was subjected to reductive phosphate tether removal utilizing LiAlH_4 to afford 1,3-*anti*-diol **2.3j**. This one-pot sequential operation enabled the stereoselective synthesis of the 1,3-*anti*-diol fragment **2.3j** in 56% yield (83% av/rxn) over three reactions in a single pot.

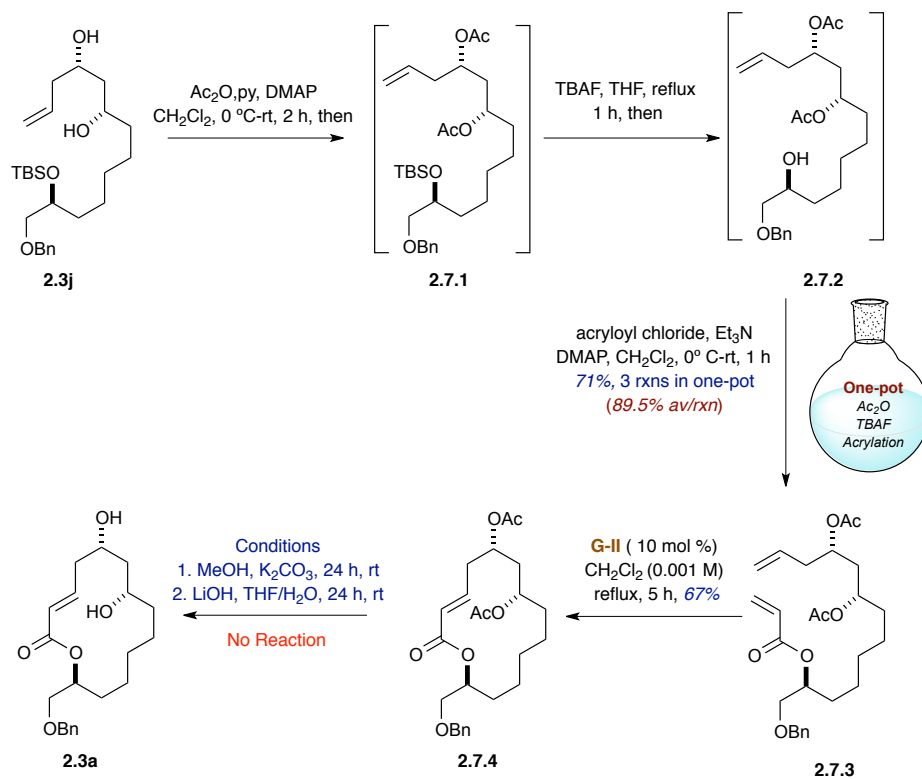
Scheme 2.6. Synthesis of TBS-protected diol **2.3j** via consecutive two one-pot sequential protocols.



The method continued with simple protecting group manipulations and acylation with acryloyl chloride to access the acrylate fragment **2.3l**. In this regard, we developed a

one-pot, sequential acetate-protection, followed by a TBS-deprotection and acrylation sequence, to access the acrylate fragment **2.7.3** (Scheme 2.7). Next, the TBS-protected diol **2.3j** was subjected to acetate-protection using Ac₂O, DMAP and pyridine in CH₂Cl₂ at room temperature. After completion of reaction, the solvent was removed under reduced pressure and the residue was dissolved in THF followed by addition of TBAF. The reaction mixture was refluxed for 1 h. After completion of reaction, the solvent was evaporated and CH₂Cl₂ was added, followed by Et₃N under inert atmosphere.

Scheme 2.7. Synthesis of macrolactone **2.3a** utilizing acetate protecting group.



The reaction mixture was lowered to 0 °C and acryloyl chloride was added dropwise, and it was stirred for 1 h. The reaction mixture was quenched with ice-cold water, extracted with CH₂Cl₂, dried (Na₂SO₄), concentrated under reduced pressure and purified with

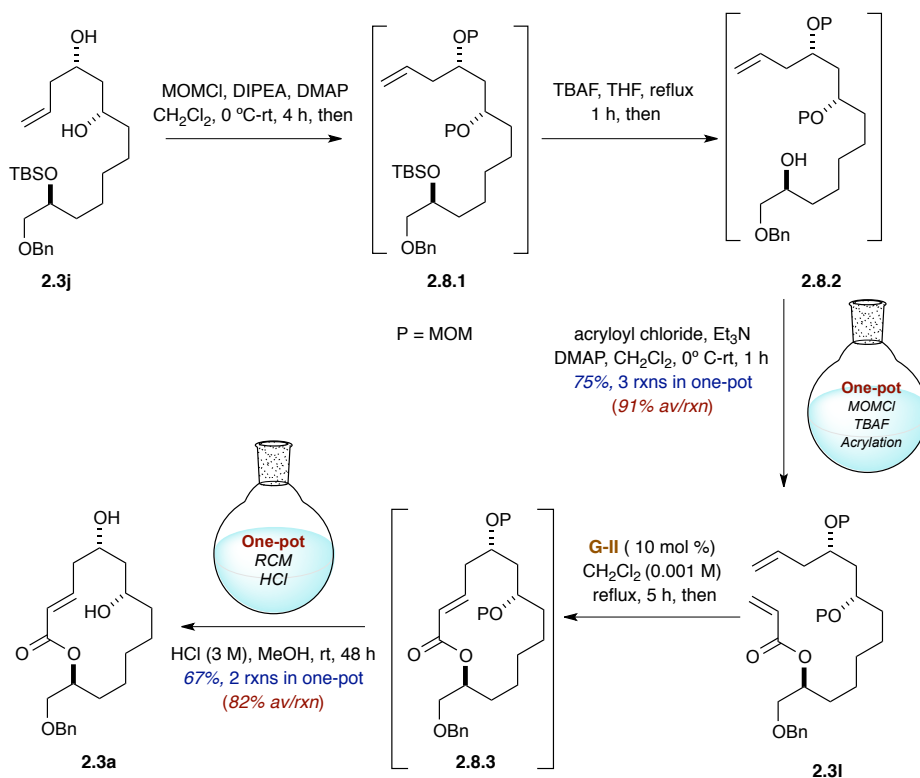
SiO₂ chromatography, which furnished the acrylate fragment **2.7.3** in 71% yield from the three-reaction sequence in a single pot. The diene fragment **2.7.3** was subsequently cyclized via RCM utilizing the **G-II** catalyst, affording acetate-protected macrolactone **2.7.4** in 67% yield. Next, we attempted various reaction conditions to remove the acetate-protecting group, but, unfortunately we were unable to generate the macrolactone **2.3a**. We observed a Michael addition to the α,β -unsaturated functionality of macrolactone **2.8.3**, which was confirmed by ¹H NMR spectroscopy.

In order to solve this issue, we replaced the acetate with a MOM-protecting group (Scheme 2.8). Thus, TBS-protected alcohol **2.3j** was subjected to a one-pot sequential MOM-protection/TBS-deprotection/acrylation sequence. In this regard, TBS-protected alcohol **2.3j** was subjected to MOM-protection utilizing MOMCl and DIPEA in CH₂Cl₂ at room temperature. After reaction completion, the solvent was evaporated and, without further purification, THF was added followed by TBAF under argon. The reaction mixture was refluxed for 1 h until complete consumption of the starting material had occurred, then the solvent was removed and the crude product was dissolved in CH₂Cl₂. Addition of Et₃N and acryloyl chloride at 0 °C generated the acrylate fragment **2.3l**. The reaction mixture was quenched with ice-cold water, extracted with CH₂Cl₂ and purified with silica gel chromatography. This one-pot, three-reaction protocol afforded the acrylate fragment **2.3l** in 75% overall yield (91% av/rxn).

To our delight, the synthesis of 14-membered macrocycle **2.3a** was accomplished in short order via a final one-pot protocol consisting of a ring-closing metathesis (RCM) and MOM-deprotection sequence. After completion of reaction, the solvent was

evaporated, and the crude product was purified through flash column chromatography, which afforded the macrolactone **2.3a** in 67% overall yield (82% av/rxn). Overall, the 14-membered α,β -unsaturated macrolactone **2.3a** was synthesized from triene (*R,R*)-**2.3g** and CM partner **2.3h** in 11.2% total yield using eleven reactions in four pots, thus significantly reducing purification events.

Scheme 2.8. *Synthesis of 14-membered macrolactone 2.3a.*

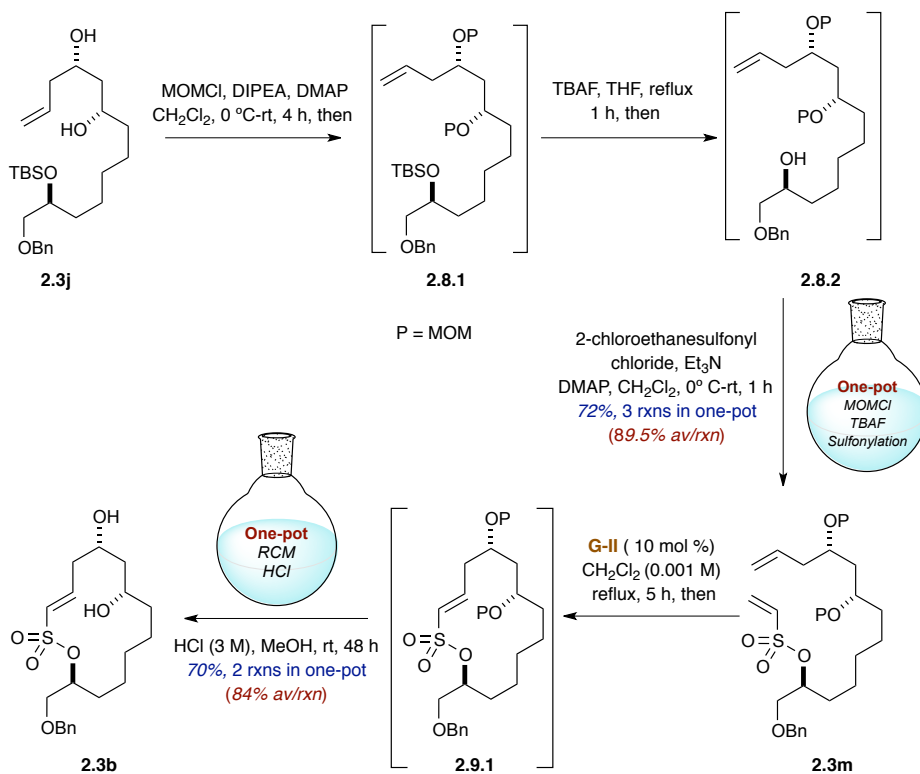


Encouraged by these results, we were next interested in exploring the applicability of our method for the generation of different sulfur and phosphorus-based derivatives of the 14-membered macrolactone. In particular, acyclic vinyl sulfonates and their analogs have a rich biological profile that has seen a resurgence of interest in the recent years due to their activities against cysteine proteases implicated in parasitic diseases⁴⁶ such as

Chagas disease, malaria, and leishmaniasis, as well as kinases involved in cancer.⁴⁷ To exploit the adaptability of our modular approach, we investigated the replacement of the acrylation reaction with a vinyl sulfonylation starting from TBS-protected diol **3.2j** (Scheme 2.9). We were pleased to find that the four-pot sequential protocol already developed for the synthesis of macrolactone **3.2a** only required swapping acryloyl chloride with 2-chloroethanesulfonyl chloride to access macrosultone analog **3.2b**.

In similar fashion, the TBS-protected diol **2.3j** was subjected to a one-pot sequential MOM-protection/TBS-deprotection to access MOM-protected alcohol **2.8.2** (Scheme 2.9).

Scheme 2.9. Synthesis of macrosultone **2.3b** via sequence of four consecutive one-pot sequential protocols.



The crude product **2.8.2** was subjected to a sulfonylation reaction using 2-chloroethanesulfonyl chloride, Et₃N and DMAP in CH₂Cl₂ (0 °C to RT) to accomplish the synthesis of vinyl sulfonate **2.3m** in a one-pot operation consisting of three reactions with 72% overall yield (89.5% av/rxn). Vinyl sulfonate **2.3m** was subsequently subjected to one-pot sequential RCM/MOM-deprotection operation to generate macrosultone **2.3b** in 70% yield over a sequence of two reactions in one-pot (84% av/rxn). Overall, both the macrolactone **2.3a** and macrosultone **2.3b** scaffolds were efficiently synthesized over a sequence of four consecutive one-pot sequential protocols with excellent overall yields. The workup and purification procedures were reduced to four steps over eleven reactions, highlighting the green nature of this method.

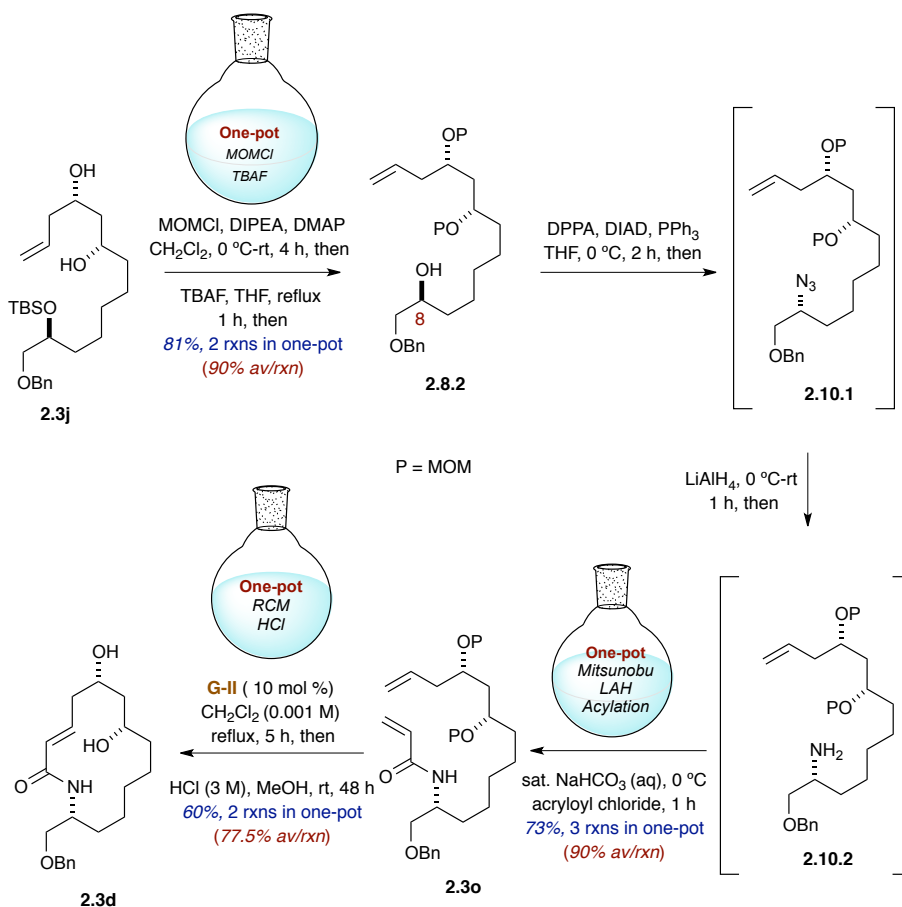
2.3.3. Synthesis of 14-membered macrolactam **2.3d** and macrosultam **2.3e** analogs

Next, we evaluated our approach for the syntheses of macrolactam **2.3d** and macrosultam **2.3e** derivatives in order to provide additional warhead diversity. On the basis of the efficiency observed during the acrylation and sulfonylation reactions in previous protocols, we anticipated the use of similar transformations to install the corresponding amine-based, α,β -unsaturated warheads in the 14-membered macrocycle. To this end, we accommodated a one-pot procedure involving a Mitsunobu reaction on the C8 carbinol (Scheme 2.3, path B), followed by azide reduction with LiAlH₄ and subsequent amine functionalization. To develop this route, we investigated the use of alkaline aqueous solutions for in situ quenching of LiAlH₄ and successive amine functionalization. In this event, we found that saturated NaHCO₃ allows for deactivation

of the reducing agent and simultaneously, provides efficient basic conditions for the addition of acryloyl chloride.

Following a one-pot, two-reaction procedure, TBS-protected diol **2.3j** was converted to MOM-protected alcohol **2.8.2** in 81% yield (Scheme 2.10). The MOM-protected alcohol **2.8.2** was subsequently subjected to another one-pot, three-reaction sequence consisting of Mitsunobu reaction/reduction/acrylation to afford the desired acrylamide fragment **2.3o**.

Scheme 2.10. *Synthesis of macrolactam analog 2.3d via a sequence of five one-pot operations.*



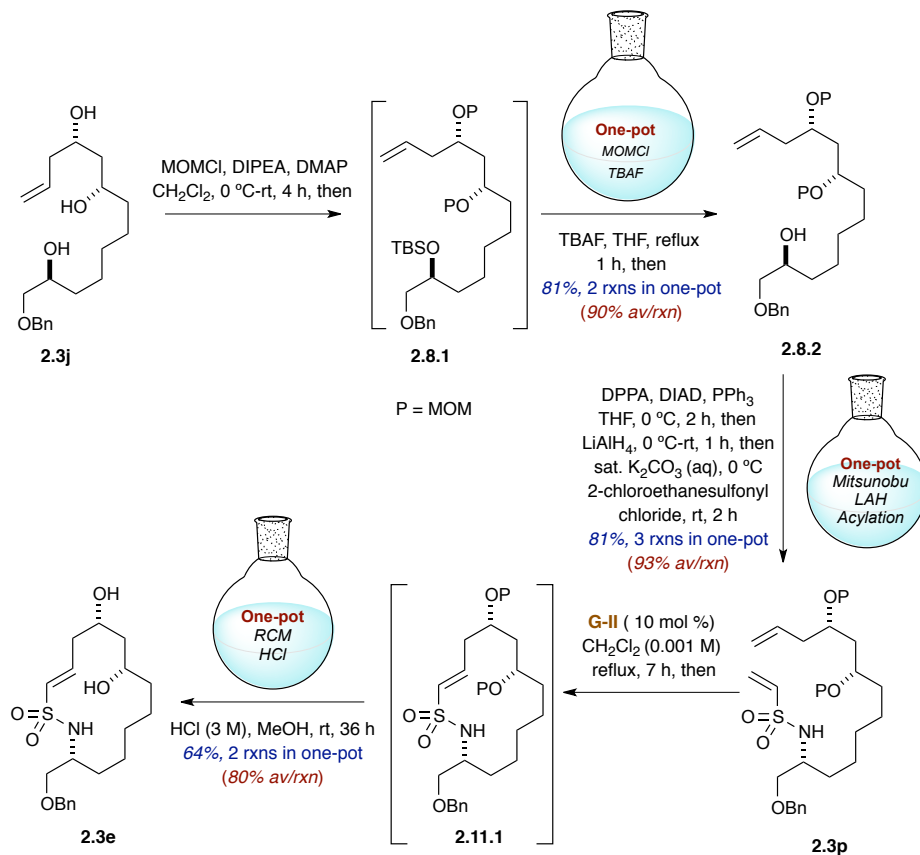
In this regard, a Mitsunobu reaction (DPPA, DIAD and PPh₃ in THF at 0 °C) was performed to convert the MOM-protected alcohol **2.8.2** to the corresponding azide fragment **2.10.1**. After completion of the Mitsunobu reaction, LiAlH₄ was added to the crude product in the same pot without any solvent change, which afforded the amine fragment **2.10.2**. Excess LiAlH₄ was quenched in situ by addition of aqueous saturated NaHCO₃, which also served as base for the subsequent reaction.

Next, we added acryloyl chloride to the crude reaction mixture and it was stirred for 1 h at 0 °C, which furnished the acrylamide **2.3o** in 73% yield over three reactions in one-pot (90% av/rxn) without any solvent adjustment. The acrylamide **2.3o** was then subjected to a final one-pot sequential RCM/MOM deprotection, which afforded macrolactam **2.3d** in 60% yield over the two reactions in one-pot. Overall, the macrolactam analog was successfully assembled in a series of five one-pot sequential-protocols using a total of only five workup and purification procedures.

Analogously, the macrosultam analog **2.3e** was obtained via a sequence of three consecutive one-pot operations starting from TBS-protected diol **2.3j** (Scheme 2.11). In similar fashion, TBS-protected alcohol **2.3j** was transformed to MOM-protected alcohol **3.8.2** via a one-pot MOM-protection/TBS-deprotection sequence. The MOM-protected alcohol was converted to the corresponding vinyl sulfonamide **2.3p** via one-pot sequential Mitsunobu/reduction/sulfonylation sequence. Applying saturated K₂CO₃ and 2-chloroethanesulfonyl chloride during the third reaction of the one-pot event, enabled the generation of sulfonamide **2.3p** in 81% overall yield (93% av/rxn) over the course of three reactions. Next, the corresponding macrosultam **2.3e** was obtained via a one-pot

RCM/MOM-deprotection sequence with a 64% yield over two reactions in one-pot (80% av/rxn).

Scheme 2.11. *Synthesis of macrosultam 2.3e via sequence of five consecutive one-pot operations.*

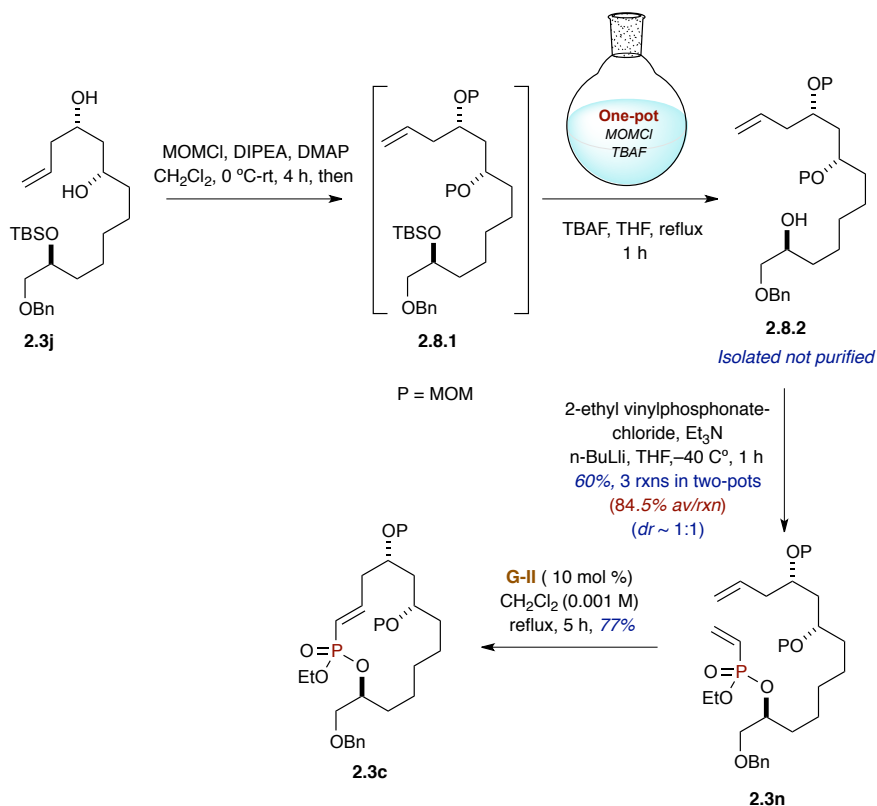


Taken collectively, both macrolactam **2.3d** and macrosultam **2.3e** analogs were efficiently synthesized via a sequence of five consecutive one-pot sequential operations from readily prepared starting materials in good to excellent yields.

2.3.4. Synthesis of 14-membered macrophostone 2.3c and macrophostam 2.3f analogs

Next, we were interested in the synthesis of related phosphorus macrocycles **2.3c** and **2.3f**, given the rich biological history of phosphorus-containing molecules.⁴⁸ The RCM precursors **2.3n** and **2.3q** were synthesized in similar fashion, with the difference of carrying out the warhead installation in a separate pot due to reagent incompatibilities (Figure 2.3). Accordingly, following a one-pot, two-reaction protocol consisting of MOM-protection followed by TBS-deprotection of **2.3j** afforded MOM-protected alcohol **2.8.2** (Scheme 2.12). The crude alcohol was then subjected to a phosphorylation reaction, which afforded an inseparable diastereomeric mixture (*dr* ~ 1:1) of **2.3n**.

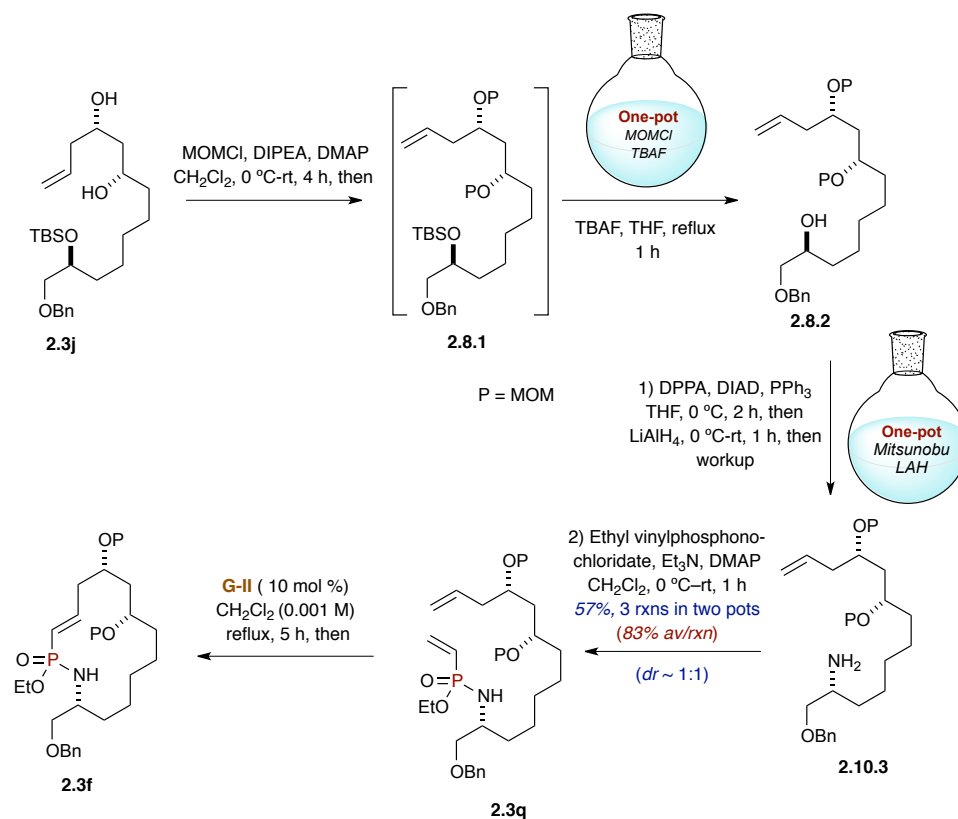
Scheme 2.12. Synthesis of macrophostone **2.3c** via sequence of five pots.



Thus, after three reactions in two pots, the P-chiral vinyl phosphonates **2.3n-*R*_P** and **2.3n-*S*_P** were obtained in 60% overall yield (84.5% av/rxn). The diastereomeric mixture was then subjected to RCM reaction utilizing the **G-II** catalyst, which furnished the MOM-protected macrophostone **2.3c** in 77 % yield.

Likewise, the P-chiral vinyl phosphonamides **2.3q-*R*_P** and **2.3q-*S*_P** were furnished in 57% over three reactions in two pots (83% av/rxn). In this regards, TBS-protected alcohol **2.3j** was subjected to a one-pot sequential MOM-protection/TBS-deprotection sequence to afford the MOM-protected alcohol **2.8.2** in 89% yield over two reactions in one-pot (Scheme 2.13).

Scheme 2.13. *Synthesis of macrophostam 2.3f over a sequence of six pots.*



A subsequent one-pot Mitsunobu/reduction sequence afforded the amine **2.10.3**. After the workup, the crude amine was subjected to a phosphorylation reaction to afford the inseparable diastereomeric mixture (*dr* ~ 1:1) of RCM precursor **2.3q**-*R_p/S_p* in 57% yield over three reaction in two-pots. In the final step, the diastereomeric mixtures underwent efficient RCM reaction to deliver α,β -unsaturated, P-stereogenic phostams **2.3f**- *R_p/S_p* in 71% yields. Overall, macrocycles **2.3c** and **2.3f** were accessed from (*R,R*)- **2.3g** and CM partner **2.3h** after conducting ten and twelve reactions, respectively, with a number of efficient processes that reduced the number of reaction pots to five and six.

2.4. Conclusion

In summary, we have disclosed a series of efficient one-pot sequential protocols that enable the asymmetric synthesis of natural product-like macrocycles bearing an α,β -unsaturated entity (**2.3a-f**).⁴⁹ The macrocycles were accessed in four- to six-pot processes from (*R,R*)-**2.3g** and CM partner **2.3h** with total yields ranging from 7.3% to 11.2%. The overall pot-economical approach is operationally simple, efficient, and library amenable. A notable merit of the method is the application of multiple consecutive pot-economic operations that significantly avoid purification procedures between successive reactions. Based on our previous applications of the RCM/CM/[“H₂”] protocol, we expect that a CM partner can be tactically chosen to assemble macrocycles with additional diversity, including various ring sizes, substituents and stereochemistries.

Further expansion of this approach for the synthesis of a variety of novel medium- and large-sized macrocycles will be reported in due course.

2.5. Special Acknowledgment

The author acknowledges that portions of this chapter, including the preliminary Introduction and Results and Discussion sections, are reprinted, in part, or adapted from the following publications, with permission from the corresponding publishers:

Javed, S.; Bodugam, M.; Ganguly, A.; Torres, J.; Hanson, P. R. Modular Synthesis of Novel Macrocycles Bearing α,β -Unsaturated Chemotypes via a Series of One-Pot, Sequential Protocols. *Chem. Eur. J.* **2016**, 22, 6755–6758.

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Chapter-3

Pot-Economical Approach for the Asymmetric Total Synthesis of
Anti-fungal Natural Product Sch-725674 and Corresponding Analogs

3.1. Introduction

The development of novel methods that enable the expedient syntheses of complex bioactive targets and corresponding analogs is important in modern day organic synthesis. In this regards, the synthesis of advanced intermediates, medicinal compounds, natural products and their synthetic analogs with minimum number of chemical operations is of prime importance. In particular, one-pot sequential protocols for the synthesis of bioactive natural product and corresponding analogs play a crucial role in the early phase of probes development and drug discovery. Accordingly, one-pot sequential protocols are gaining popularity¹ as a powerful tool to achieve the syntheses of complex bioactive medicinal agents.^{2,3} Among several featured publications, Hayashi and coworkers have employed consecutive, one-pot sequential protocols for the streamlined synthesis of representative examples of these targets.⁴ In this regard, they were able to complete the multi-reaction syntheses of (–)-oseltamivir,^{2a,b} prostaglandin A₁ and E₁ methyl esters,^{2c} (–)-horsfiline and (–) coerulescine^{3a} in step- and pot-economical manner. A later synthesis of (–)-oseltamivir⁵ was accomplished in a one-pot operation. In similar fashion, the syntheses of ABT-341^{2d} and (S)-baclofen⁶ were accomplished via a one-pot protocol.

As part of our ongoing efforts to develop efficient methods for the synthesis of complex target molecules,^{3b-d} we have recently reported a modular syntheses of novel macrocycles possessing α,β -unsaturated chemotypes employing a series of one-pot sequential protocols (Figure 1).⁷ This efficient and library amenable method utilizes four to six consecutive one-pot sequential operations. We highlighted a phosphate tether-mediated asymmetric approach for the synthesis of a series of novel carbon-, sulfur- and

phosphorus-based macrocycles **3.1c–e** (Figure 3.1). Encouraged by the aforementioned literature precedence^{2,3,4,5} and motivated by the efficiency of our previously developed one-pot sequential protocols, Chapter 3 highlights our recent disclosure of an enantioselective total synthesis of antifungal natural product Sch-725674 (**3.1f**) and its analogs **3.1g–k** (Figure 3.1).^{3d}

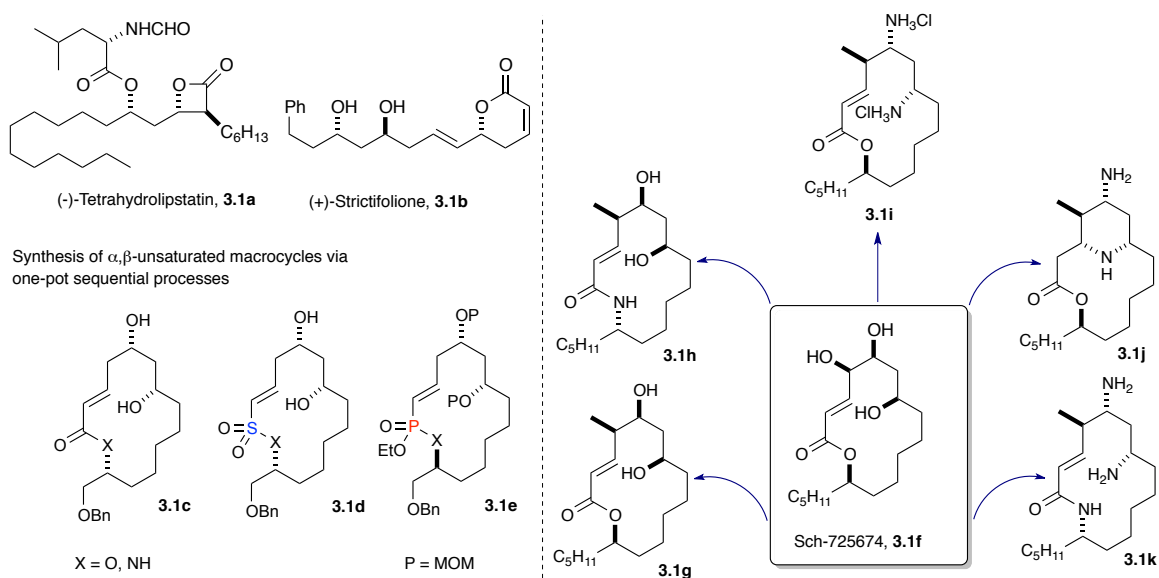


Figure 3.1. Sch-725674 (**3.1f**) and corresponding analogs **3.1g–k**.

3.1.1. Sch-725674 and related natural products

Sch-725674 (**3.1f**), an antifungal macrolide, was isolated from a culture of *aspergillus sp* and structurally elucidated in 2005 by Yang and co-workers.⁸ This natural product exhibits activity against *saccharomyces cerevisiae* and *candida albicans* with MIC values of 8 and 32 $\mu\text{g/mL}$, respectively. Key structural features of **3.1f** include a 14-membered macrolactone ring, an *E*-configured α,β -unsaturated ester, a lipophilic *n*-pentyl side chain and a 1,3-*anti*-diol moiety embedded within a four-carbon (C4–C7) subunit containing three stereogenic carbinol centers (Figure 3.2). An intriguing feature of **3.1f** is

the absence of commonly found methyl groups on the backbone of macrolide antibiotics erythromycin (**3.2a**) and narbomycin (**3.2b**). The closest structural relatives of Sch-725674 are the self-germination inhibitor gloeosporone⁹ (**3.2c**) and the recently isolated gliomasolides A to E (**3.2d–h**),¹⁰ which show cytotoxic activity against the growth of HeLa cell lines (Figure 3.2), thus making **3.1f** a potentially attractive biological and synthetic target.

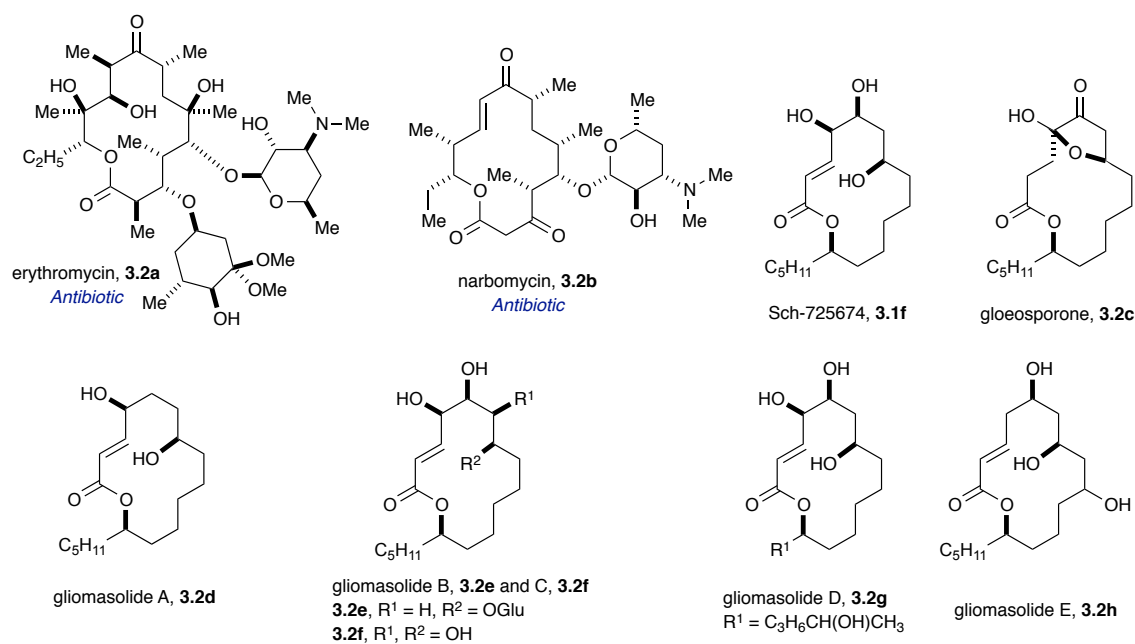


Figure 3.2. Natural product macrolactones Sch-725674, gloeosporone, **3.2c** and gliomasolides A-E, **3.2d–3.2h**.

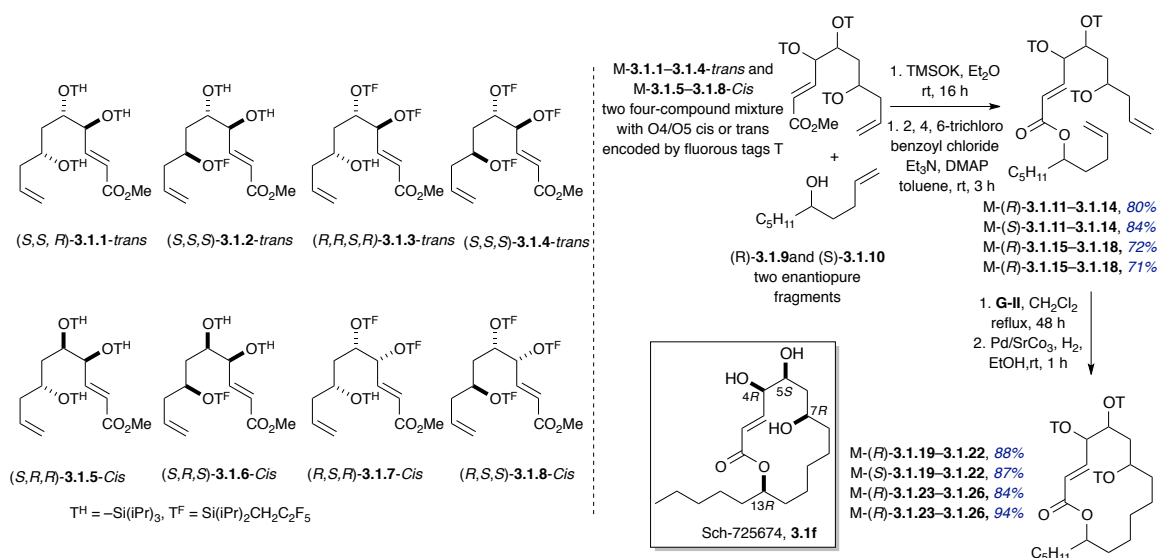
3.2. Overview of previous total synthesis of Sch-725674 (**3.1f**)

Due to anti-fungal activity and novel structural features, Sch-725674 has attracted significant attention from several synthetic groups. The asymmetric total synthesis of Sch-725674 has been reported by Curran,¹¹ Prasad,^{12,13} Kaliappan¹⁴ and recently by Reddy and coworkers.¹⁵ For the purpose of this chapter, only key features of the synthetic strategies toward the synthesis of Sch-725674 will be discussed.

3.2.1. Synthesis of a 16-stereoisomers library of Sch-725674 using a fluorous tagging strategy

In 2012, the Curran group reported an elegant synthesis of a library of all 16 possible stereoisomers of Sch-725674 (**3.1f**) utilizing a fluorous tagging approach developed in their group (Scheme 3.1).¹¹ This strategy involved the syntheses of two mixtures of four fluorous-tagged quasi-isomers¹⁶ **M-3.1.1–3.1.4-trans** and **M-3.1.5–M-3.1.8-cis** and two enantiopure fragments of (*R*)-**3.1.9** and (*S*)-**3.1.10**.

Scheme 3.1. Synthesis of complete stereoisomer library of Sch-725674 (**3.1f**) using fluorous tagging strategy.



Starting with **M-3.1.1–M-3.1.4-trans** series, the authors hydrolyzed the methyl ester of **M-3.1.1–M-3.1.4-trans** compounds using TMSOK and the acids obtained were divided into two flasks. Each half portion of **M-3.1.1–M-3.1.4-trans** were coupled with either (*R*)-**3.1.9** or (*S*)-**3.1.10** under Yamaguchi reaction conditions, which afforded the RCM precursors (**M-3.1.11–M-3.1.18-trans**) in good yield (74%–84%). Ring-closing metathesis of diene (**M-3.1.11–M-3.1.18-trans**), followed by regioselective

hydrogenation with poisoned Pd catalyst, furnished the final tagged quasi-isomeric mixtures of **M-3.1.19–M-3.1.22-*trans*** in good to excellent yields.

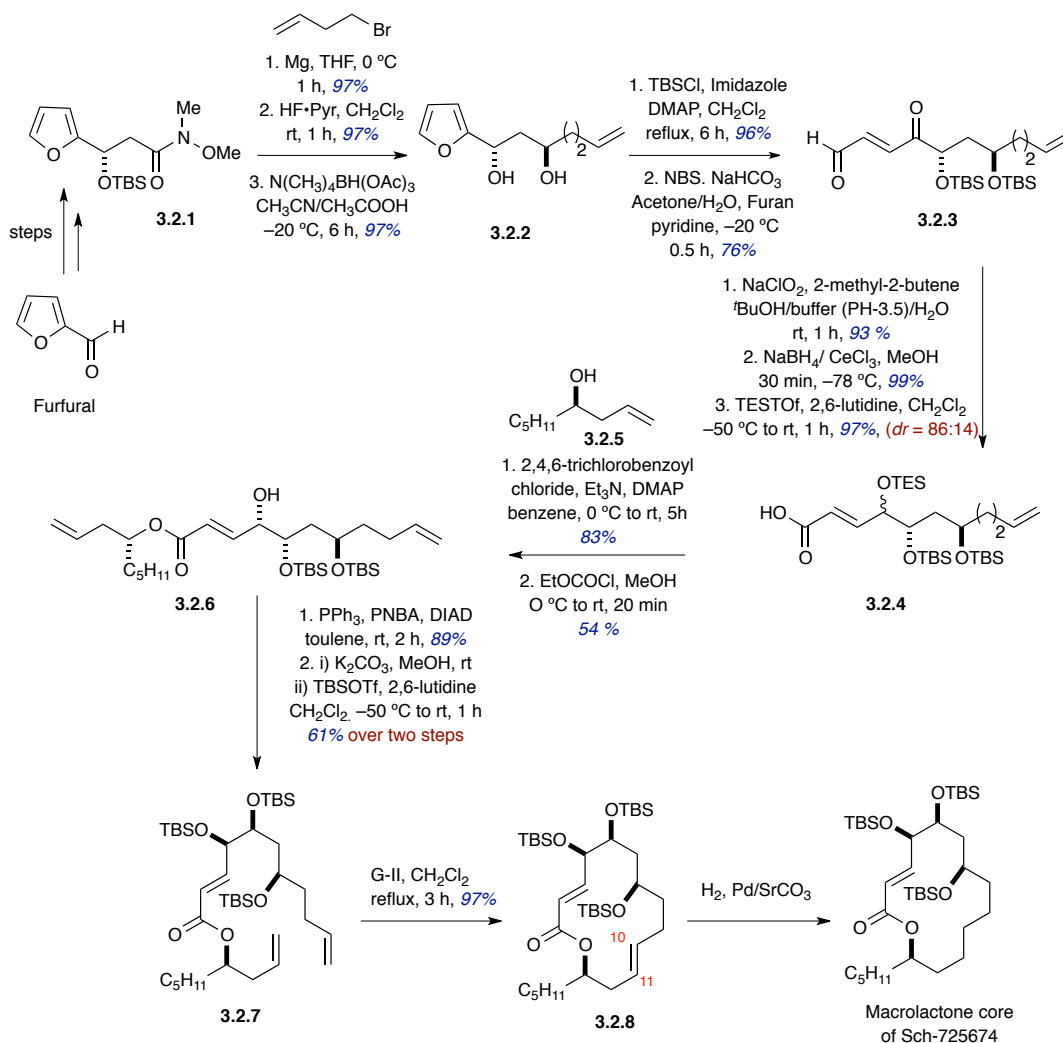
In similar fashion, the **M-3.1.5–M-3.1.8-*cis*** series of isomers were converted to the final tagged quasi-isomeric mixtures **M-3.1.23–M-3.1.26-*cis***. After separation, tag-cleavage and purification of the final compounds with chiral HPLC afforded the penultimate precursors of the 16 true stereoisomers of Sch-725674. The complete stereochemical configuration (*4R,5S,7R,13R*) of Sch-725674 was assigned by Curran and coworkers, and was based on the comparison of spectral data of the synthesized 16 stereoisomers with the published spectra⁸ of **3.1f**.

3.2.2. An asymmetric synthesis of macrolactone core of Sch-725674

In 2014, Prasad *et al* reported an enantioselective synthesis of the macrolactone core of Sch-725674 from commercially available furfural using RCM as a key reaction (Scheme 3.2).¹² The synthesis of Weinreb amide **3.2.1** was accomplished according to literature procedures.¹⁷ Grignard addition to Weinreb amide **3.2.1** followed by stereoselective reduction,¹⁸ utilizing $\text{Me}_4\text{N}(\text{OAc})_3\text{BH}$ to provide the 1,3-diol fragment **3.2.2** in 97% yield. TBS-protection of both hydroxy groups in **3.2.2** using TBSCl/imidazole, followed by oxidation of the furan with NBS/ NaHCO_3 proceeded smoothly to furnish keto-aldehyde **3.2.3** in 76% yield. Aldehyde **3.2.3** was further oxidized to the corresponding carboxylic acid in 93% yield. Stereoselective reduction of the ketone function in **3.2.3** under Luche reduction conditions¹⁹ afforded the alcohol in quantitative yield, which was subsequently protected using TESOTf, 2,6-lutidine to afford the TES-protected alcohol **3.2.4** in 97% yield.

Next, the authors coupled acid **3.2.4** with homoallylic alcohol **3.2.5**²⁰ under Yamaguchi reaction conditions, followed by selective TES-deprotection using EtOCOCl in MeOH, to furnish alcohol fragment **3.2.6** in 54% yield. Mitsunobu inversion of alcohol **3.2.6** generated the *p*-nitrobenozate in 83% yield, which was subsequently subjected to deprotection under basic conditions (K₂CO₃, MeOH), followed by TBS-protection, to afford RCM precursor **3.2.7** in good yield.

Scheme 3.2. *Enantioselective synthesis of macrolactone core of Sch-725674.*



Ring-closing metathesis of the diene **3.2.7** using **G-II** catalyst afforded the macrolactone core **3.2.8** in 97% yield. After screening different reaction conditions for the reduction of C–C double bond at C10–C11 position of **3.2.8**, the authors were unable to attain the desired reduced product. However, the authors reported that the required selective hydrogenation of the C–C double could be accomplished by employing the reduction conditions reported by Curran's and coworker (H_2 , Pd/SrCO₃)¹¹, Which would complete the synthesis of the macrolactone core of Sch-725674.

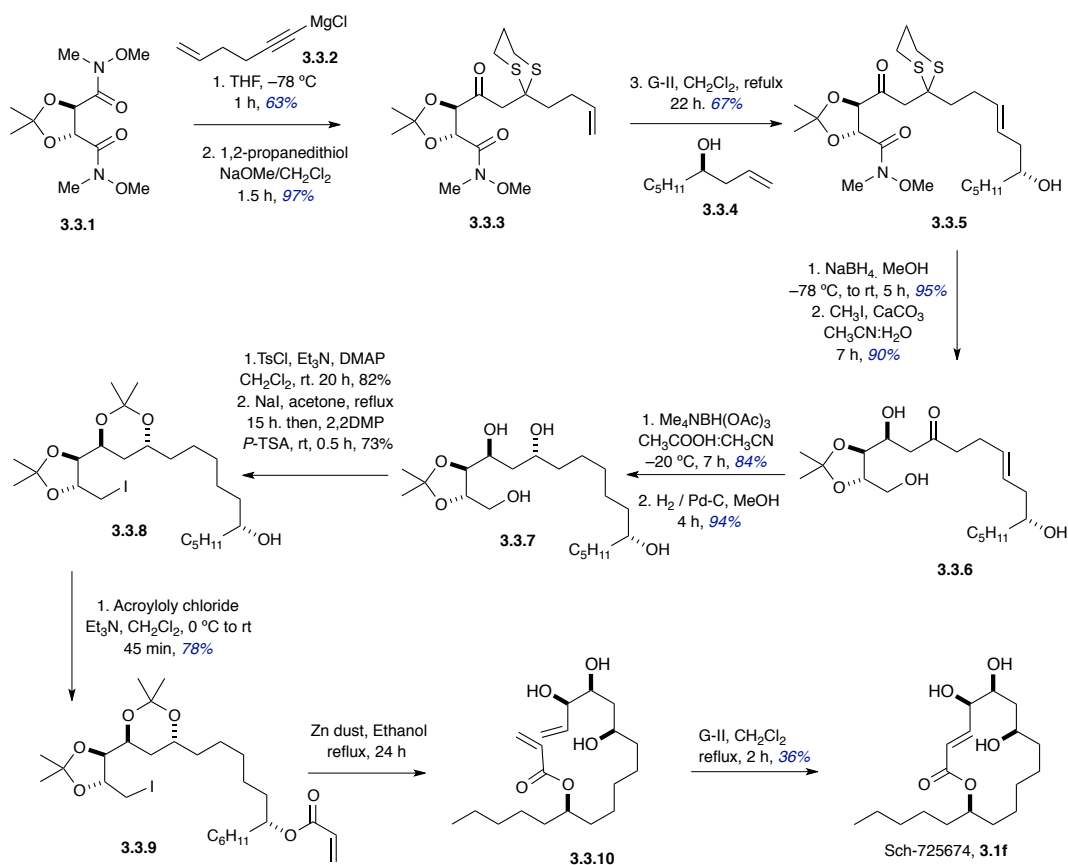
3.2.3. An enantioselective total synthesis of Sch-725674

In 2014, Prasad and coworker reported an enantiospecific total synthesis of Sch-725674 (**3.1f**) beginning with commercially available L-(+)-tartaric acid (Scheme 3.3).¹³ The three key features of the synthesis were utilization of Ley's dithiaketalization of an alkynone, Boord olefination and RCM. The forward synthesis of Sch-725674 began with Grignard addition of **3.3.2** to the *bis*-Weinreb amide **3.3.1**, which furnished an alkynyl ketone. Subsequent dithianylation of the ketone, under Ley's conditions, furnished 1,3-dithianyl ketone **3.3.3** in quantitative yield. Cross metathesis of olefin **3.3.3** with chiral homoallylic alcohol **3.3.4**²¹ using the **G-II** catalyst (3 mol%) afforded the extended alkene **3.3.5** in 67% yield.

Next, the authors carried out a stereoselective reduction of the ketone moiety in **3.3.5** using excess of NaBH₄, which not only furnished the secondary alcohol but also removed the *bis*-Weinreb amide to generate the triol moiety in quantitative yield. Dithaine-deprotection of the ketone functionality in **3.3.5** using MeI and CaCO₃ furnished the β-hydroxy ketone fragment **3.3.6** in 90% yield. Stereoselective reduction of ketone in **3.3.6** using Me₄N(OAc)₃BH (Evan's reagent)²² afforded the 1,3-*anti*-diol

fragment in good yield. Subsequent hydrogenation of the C–C double bond in the 1,3-*anti*-diol subunit using H₂/Pd-C furnished the tetrol fragment **3.3.7** in 94% yield. Selective tosylation of the primary alcohol in **3.3.7**, followed by iodination of the resulting tosylate, afforded the iodide fragment **3.3.8**, which was subsequently subjected to acrylation followed by Boord olefination (Zn, EtOH) to furnish the RCM precursor **3.3.10**. Ring-closing metathesis of diene **3.3.10** bearing three free hydroxyl groups utilizing the **G-II** catalyst furnished Sch-725674 (**3.1f**) in 36% yield. In summary, the asymmetric total synthesis of Sch-725674 was accomplished in a route with a longest linear step (LLS) sequence of 12 steps, and with 2.6% overall yield starting from the *bis*-Weinreb amide of L-(+)-tartaric acid (**3.3.1**).

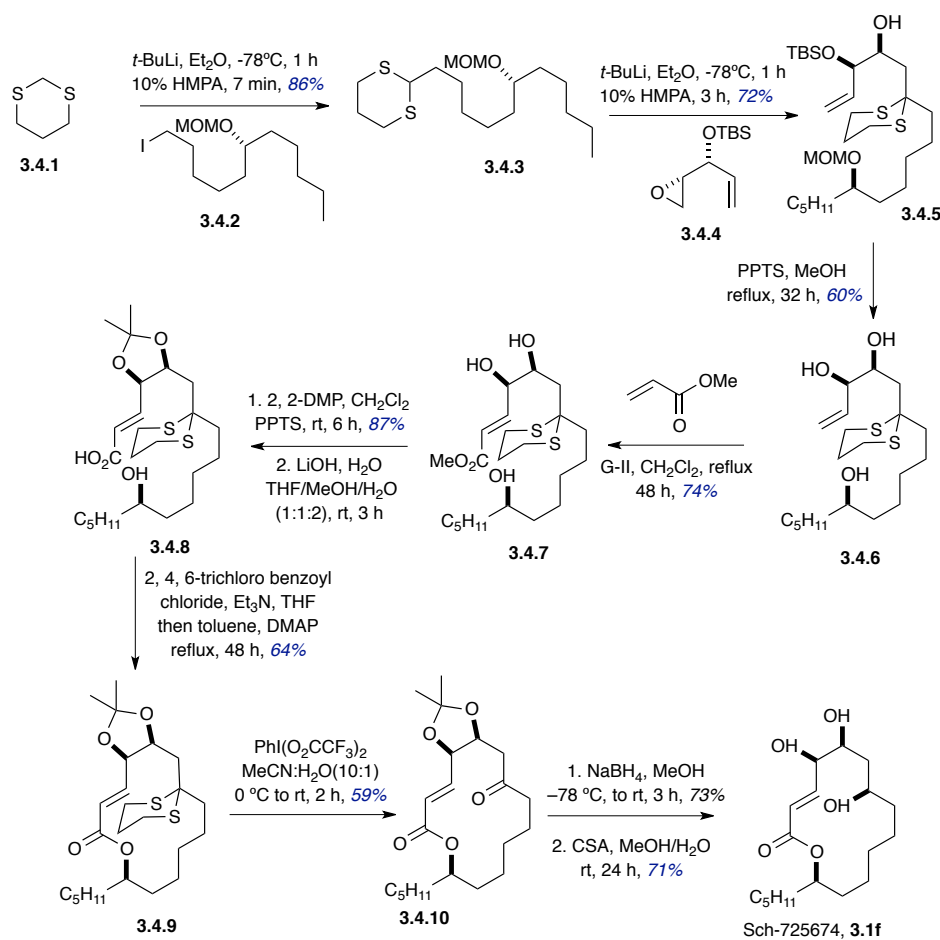
Scheme 3.3. *Enantioselective total synthesis of Sch-725674.*



3.2.4. An asymmetric total synthesis of Sch-725674

In 2015, Kaliappan and coworkers reported an enantioselective total synthesis of Sch-725674 in a route featuring an LLS of 13 steps (Scheme 3.4).¹⁴ The three key reactions involved in the synthesis of Sch-725674 (**3.1f**) were a step-wise dithiane alkylation, a cross metathesis and Yamaguchi macrolactonization. The forward synthesis of **3.1f** commenced with the synthesis of iodide **3.4.2** from commercially available (*S*)-2-(chloromethyl)oxirane.

Scheme 3.4. Enantioselective total synthesis of Sch-725674, **3.1f**.



Stepwise alkylation of 1,3 dithiane **3.4.1** with iodide **3.4.2** as the first electrophile to

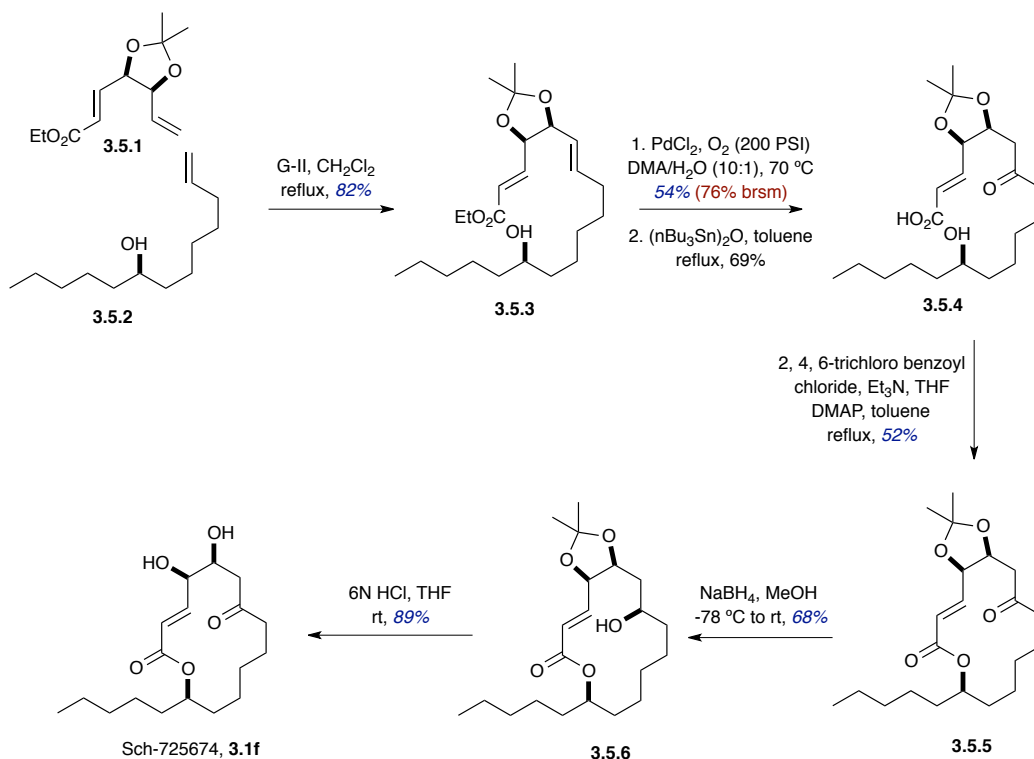
provide the intermediate **3.4.3** in 86% yield, followed by reaction with the second electrophile **3.4.4** to generate dialkylated product **3.4.5** with 72% yield. MOM and TBS-deprotection using PPTS and MeOH furnished the triol fragment **3.4.6** in 60% yield. The resulting alkene fragment **3.4.6** was subsequently subjected to CM with methyl acrylate as a CM partner using the **G-II** catalyst (15 mol%) to afford *E*-methyl ester **3.4.7** in 74% yield. Acetonide protection of 1,2-diol in **3.4.7** using 2,2-DMP, followed by hydrolysis of the methyl ester, afforded the acid **3.4.8**. Yamaguchi macrolactonization²³ of acid **3.4.8**, followed by dithiane deprotection, using Stork's reagent,²⁴ furnished the macrolactone core of Sch-725674, **3.4.10**, in 59% yield. Stereoselective reduction of the carbonyl function in **3.4.10** using NaBH₄, followed by acetonide deprotection using CSA, furnished Sch-725674 in 71 % yield through the last step. Overall, the asymmetric synthesis of Sch-725674 (**3.1f**) was accomplished in 13 steps from a known alcohol.²⁸

3.2.5. Formal total synthesis of Sch-725674

More recently, Reddy and coworkers reported the formal total synthesis of Sch-725674 (Scheme 3.5).¹⁵ The forward synthesis of **3.1f** began with CM of known acetonide-protected alkene **3.5.1**²⁵ and pre-synthesized alcohol **3.5.2**,²⁶ which afforded the ester fragment **3.5.3** with good yield (82%) and excellent *E*-selectivity. After screening different reaction conditions, the desired ketone was obtained using Wacker oxidation²⁷ of C–C double bond in **3.5.3** using O₂ (200 Psi) and PdCl₂. Subsequent hydrolysis of the ester using bis(tributyltin)oxide in refluxing toluene furnished the seco-acid **3.5.4** in 69% yield. Yamaguchi macrolactonization of seco-acid **3.5.4** using 2,4,6-trichlorobenzoyl chloride and DMAP in refluxing toluene yielded the macrolactone **3.5.5** in 52% yield. Stereoselective reduction of the ketone moiety in **3.5.5** using NaBH₄

followed by acetonide deprotection using 6N HCl completed the formal total synthesis of Sch-725674 by an efficient series of steps.

Scheme 3.5. *The formal total synthesis of Sch-725674, 3.1f.*



3.3 Results and discussion

3.3.1 Proposed retrosynthetic analysis of Sch-725674

Retrosynthetic analysis revealed that Sch-725674 (**3.1f**) could be assembled via RCM of diene **3.3a** (Figure 3.3). Derivation of the RCM precursor **3.3a** was planned using two consecutive one-pot sequential protocols from epoxide **3.3b**, namely a Finkelstein substitution/Boord olefination/acetonide deprotection procedure and a one-pot two-reaction sequence involving tosylation and acrylation reaction. Epoxide **3.3b** was synthesized from allylic alcohol **3.3c** *via* Sharpless asymmetric epoxidation (SAE). The allylic alcohol in turn was accessed via reductive tether removal, followed by acetonide

protection of bicyclic phosphate **3.3d**. The bicyclic phosphate **3.3d** in turn, was obtained from triene phosphate (*S,S*)-**3.3f** following a one-pot RCM/CM/chemoselective hydrogenation sequence utilizing **3.3e**²⁸ as the cross metathesis (CM) partner. This one-pot three-reaction sequence enabled the installation of the requisite C13 *n*-pentyl side chain and the C5–C7 1,3-*anti*-diol subunit. A salient feature of this approach is the modular installation of the C9–C13 fragment via CM, as well as introduction of the acrylate at a later stage, opening opportunities for future analog generation.

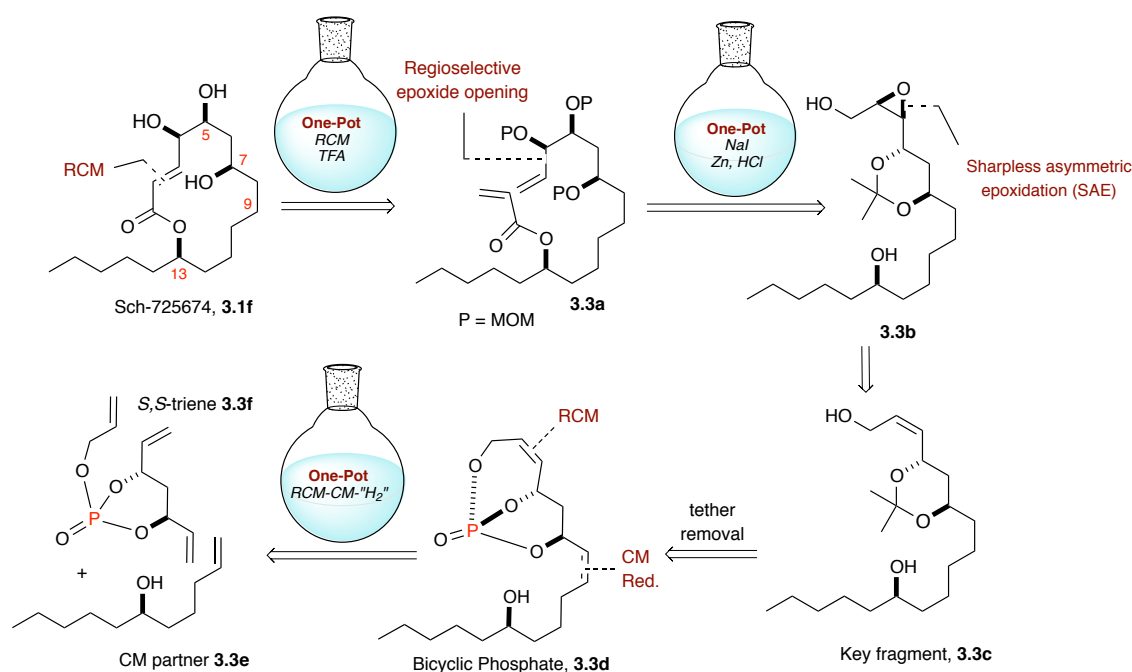


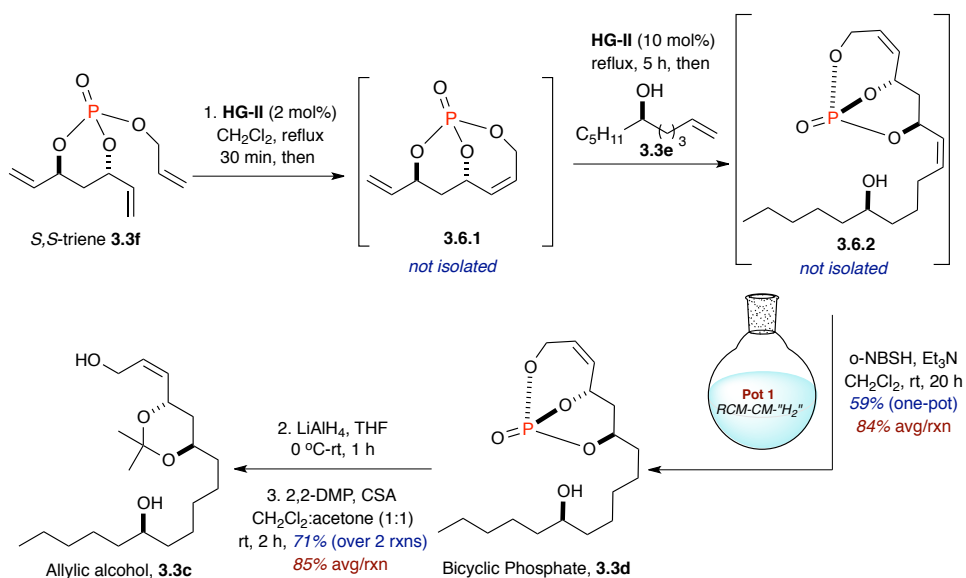
Figure 3.3. Retrosynthetic analysis of Sch-725674, **3.1f**.

3.3.2. Forward synthesis of Sch-725674

The forward synthesis of Sch-725674 (**3.1f**) commenced with the previously developed one-pot sequential RCM/CM/[H_2] protocol.²⁹ (*S,S*)-Triene **3.3f**³⁰ was subjected to RCM using the Hoveyda-Grubbs second-generation catalyst (**HG-II**)³¹ (2 mol%) in refluxing CH_2Cl_2 (Scheme 3.6). After completion of the RCM reaction (30 min), solvent was evaporated and CM partner **3.3e**²⁸ was dissolved in 1,2-dichloroethane

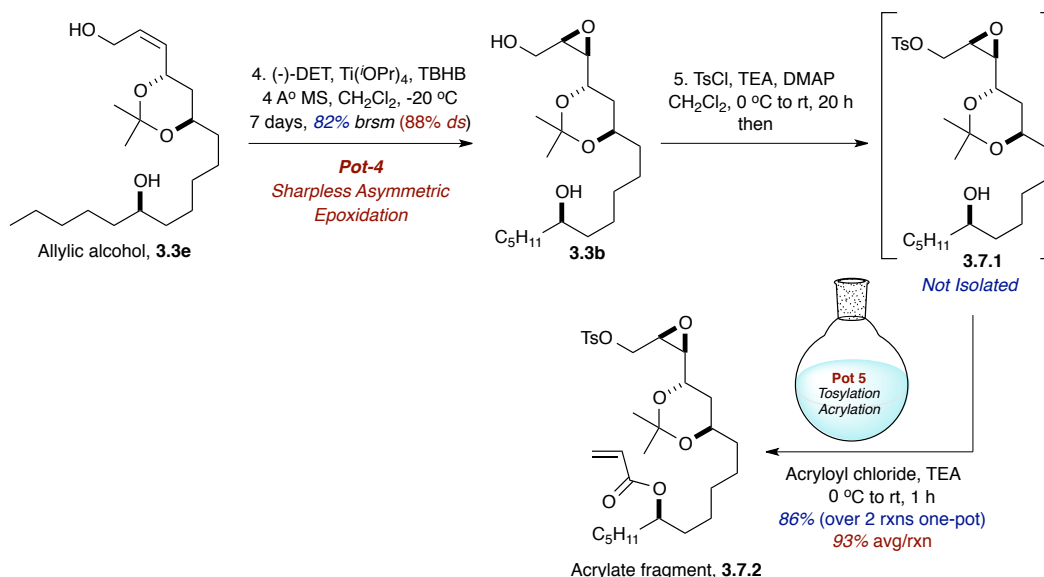
(DCE)³² and introduced to the same pot under argon, followed by addition of the **HG-II** catalyst (10 mol%). After the CM event had proceeded for 5 h at 70 °C, chemoselective diimide reduction of the external olefin in bicyclic phosphate **3.6.2** was performed by addition of *o*-nitrobenzenesulfonylhydrazine (*o*-NBSH)³³ and Et₃N (2 mL/g of *o*-NBSH) to the reaction mixture. This one-pot, three-reaction sequence provided bicyclic phosphate **3.3d** in 59% overall yield, equivalent to an average yield of 84% per reaction (84% av/rxn). Next, reductive conditions (LiAlH₄, THF, 0 °C), were used to remove the phosphate tether in **3.3d** (Scheme 3.6). The corresponding tetrol was obtained in high purity following the Fieser workup,³⁴ and, without chromatography purification, the crude 1,3-*anti*-diol was subjected to a selective acetonide protection. The crude tetrol was treated with 2,2-dimethoxypropane (2,2-DMP) and catalytic amounts of camphorsulfonic acid (CSA) as outlined in Scheme 3.6, providing 1,3-acetonide **3.3c** in 71% yield over two reactions in two pots.

Scheme 3.6. *Synthesis of acetonide protected alcohol 3.3c.*



The acetonide-protected allylic alcohol was next subjected to Sharpless asymmetric epoxidation (SAE)³⁵ by treatment with (-)-diethyl tartrate (DET), Ti(Oi-Pr)₄, cumene hydroperoxide,³⁶ which afforded the corresponding diastereomeric epoxide products in 72% yield (80% brsm) with **3.3b** as the desired major diastereomer (88% ds)³⁷ (Scheme 3.7). Following the successful assembly of epoxide **3.3b** in scalable quantities, a second one-pot protocol consisting of tosylation and acrylation sequence was applied. To this end, the primary alcohol in **3.3b** was chemoselectively transformed overnight to tosylate (TsCl, Et₃N, DMAP) in the presence of the C13 carbinol. Next, acryloyl chloride was simply added to the same pot at 0 °C to afford the acrylate fragment **3.7.2** in 86% yield for these two reactions in one-pot (93% avg/rxn).

Scheme 3.7. *Synthesis of acrylate fragment 3.7.2.*

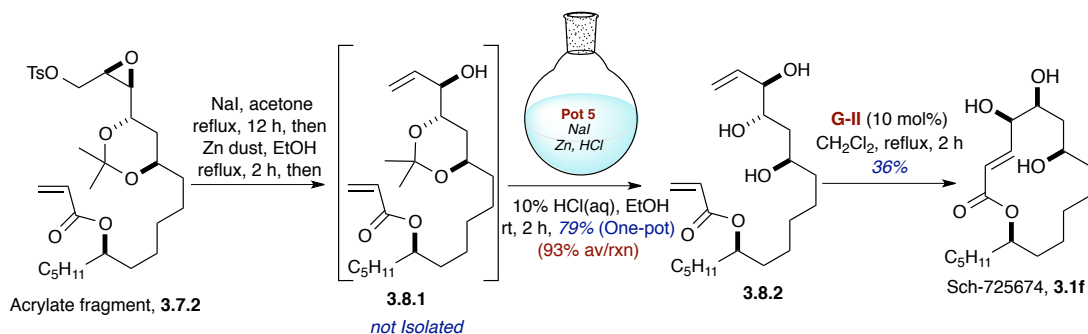


A subsequent one-pot protocol was established by subjecting **3.7.2** to a Finkelstein substitution, Boord olefination (Zn, EtOH), and acetonide deprotection sequence to assemble triol **3.8.2** (Scheme 3.8). This three-reaction, one-pot process

commenced by exposing the tosyl group in **3.7.2** to Finkelstein conditions (NaI, acetone, reflux) followed by a solvent change from acetone to ethanol and addition of activated zinc powder under reflux to promote Boord elimination over a 2 h period. Final addition of HCl at room temperature released the 1,3-anti-diol to deliver triol **3.8.2** in 79% yield over three reactions in a single pot operation (93% av/rxn).³⁸

With **3.8.2** in hand, the synthesis of Sch-725674 (**3.1f**) was accomplished via a final RCM as reported by Prasad and coworkers, the structural characterization of Sch-725674 was in good accord with data reported by Prasad and coworkers.¹³ Overall, the total synthesis of **3.1f** was accomplished in seven pots from the readily prepared triene (*S,S*)-**3.3f** and the olefin **3.3e**. Chromatography isolations were also reduced to six procedures, which saved time and minimized chemical waste generation.

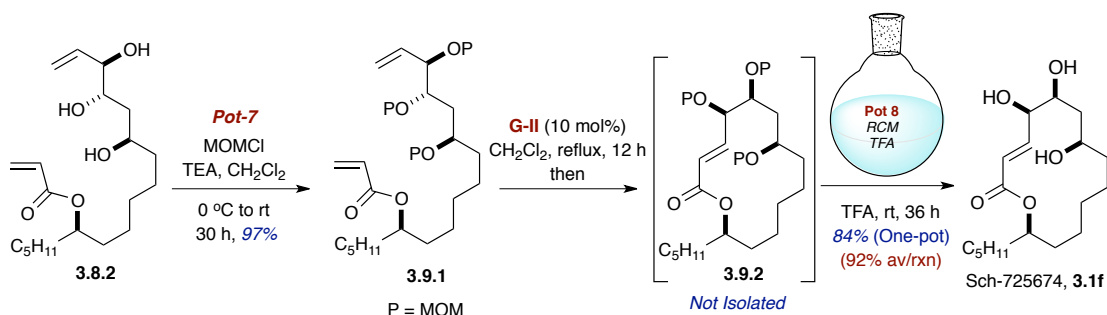
Scheme 3.8. End game; synthesis of Sch-725674.



While we were unable to match the reported 36% yield for the RCM reaction,¹³ we found that simple protection of the alcohols significantly increased the efficiency of this final macrocyclization event via RCM reaction (Scheme 3.9). In this regard, we developed a two-reaction, one-pot sequential method that consisted of RCM and methoxymethyl (MOM) deprotection to further streamline the synthesis toward **3.1f**. To this end, the carbinols in **3.8.2** were protected as MOM-ethers and the tri-protected diene

3.9.1 was obtained in 97% yield after treating with MOMCl under basic conditions. Next, the one-pot protocol began by treating metathesis precursor **3.9.1** with the **GII**³⁹ catalyst (10 mol%) in refluxing CH₂Cl₂. After completion of the metathesis event (12 h), the solvent volume was reduced and MOM-deprotection proceeded smoothly by adding trifluoroacetic acid to the same pot, delivering Sch-725674 (**3.1f**) in 84% yield over two-reactions in one-pot (92% av/rxn). This alternative approach considerably improved the yield of the RCM event, providing Sch-725674 in 14.6% overall yield from triene (*S,S*)-**3.3f** and CM partner **3.3e** following eight pots and seven chromatography purifications.

Scheme 3.9. Completion the synthesis of Sch-725674 with improved yield of RCM reaction.



Taken collectively, we disclosed a pot-economical synthetic route to the antifungal natural product Sch-725674. Overall, a seven-pot route was developed from readily prepared phosphate triene (*S,S*)-**3.3f** and olefin fragment **3.3e** and included seven isolations and six chromatography purifications. Key to the strategy is the application of a phosphate tether-mediated one-pot sequential RCM/CM/hydrogenation process, a one-pot tosylation/acrylation sequence, and a one-pot sequential Finkelstein reaction/Boord olefination/acetonide deprotection protocol. An alternative approach was introduced at the final stage of the synthesis involving a one-pot sequential RCM/MOM-deprotection protocol to overcome efficiency challenges during the macrocyclization event. Taken

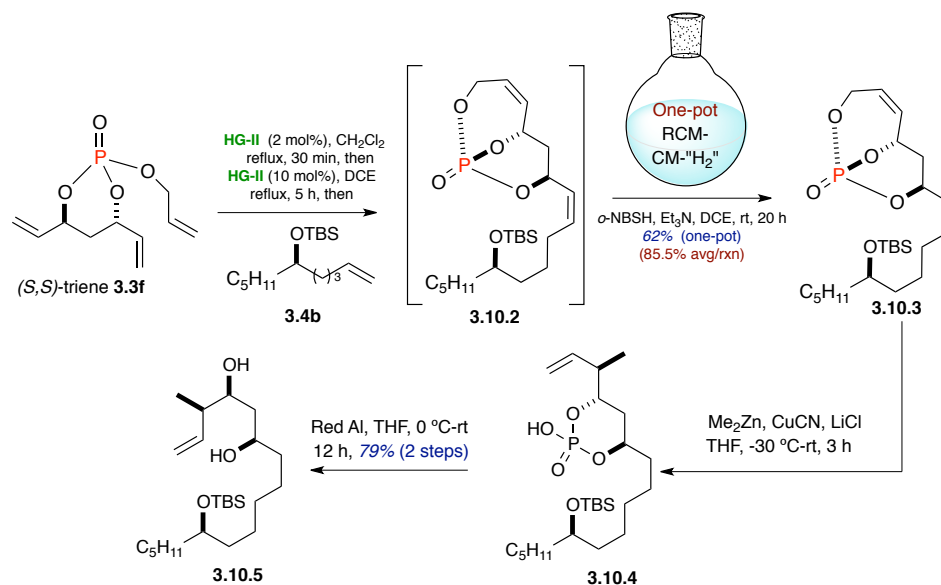
The key reactions involved in the synthesis of Sch-analogs (**3.1g–3.1k**) are one-pot sequential RCM/CM/“H₂”, one-pot sequential protecting group manipulation, Mitsunobu/reduction/acrylation and a final one-pot sequential RCM/deprotection. Starting from readily prepared (*S,S*)-triene-**3.3f** and CM partner **3.4b**, we were able to accomplish the synthesis of five structurally diverse analogs (**3.1g–3.1k**) of Sch-725674 (**3.1f**) in five–seven pots with a total of ten–thirteen reactions requiring only five–seven workup and purification procedures, respectively. All five Sch-analogs have been submitted for antifungal and antibacterial screening to our biological collaborators.

3.4.1. Syntheses of macrolactone 3.1g and macrolactam 3.1h analogs of Sch-725674

The synthesis of macrolactone analog **3.1g** began with our previously optimized phosphate tether-mediated one-pot sequential RCM/CM/“H₂”²⁹ protocol (Scheme 3.10). (*S,S*)-triene **3.3f** was cyclized via RCM reaction using **HG-II** catalyst, after completion of RCM reaction, the solvent was evaporated and CM partner **3.4b** was introduced in DCE followed by **HG-II** catalyst (10 mol%) and the reaction mixture was heated at 70 °C for 5 h. After completion of CM event, the reaction mixture was brought to room temperature and the crude product was subjected to a chemoselective hydrogenation reaction using *o*-NBSH and Et₃N (2 mL/g of *o*-NBSH).³³ This one-pot three-reaction sequence afforded the bicyclic phosphate **3.10.3** in 62% yield with 85.5% av/rxn. Regio- and diastereoselective allylic cuprate displacement reaction of bicyclic phosphate **3.10.3** utilizing CuCN, LiCl and Me₂Zn afforded the monocyclic phosphate **3.10.4**. The crude acid **3.10.4** obtained was subsequently subjected to phosphate tether removal using Red-

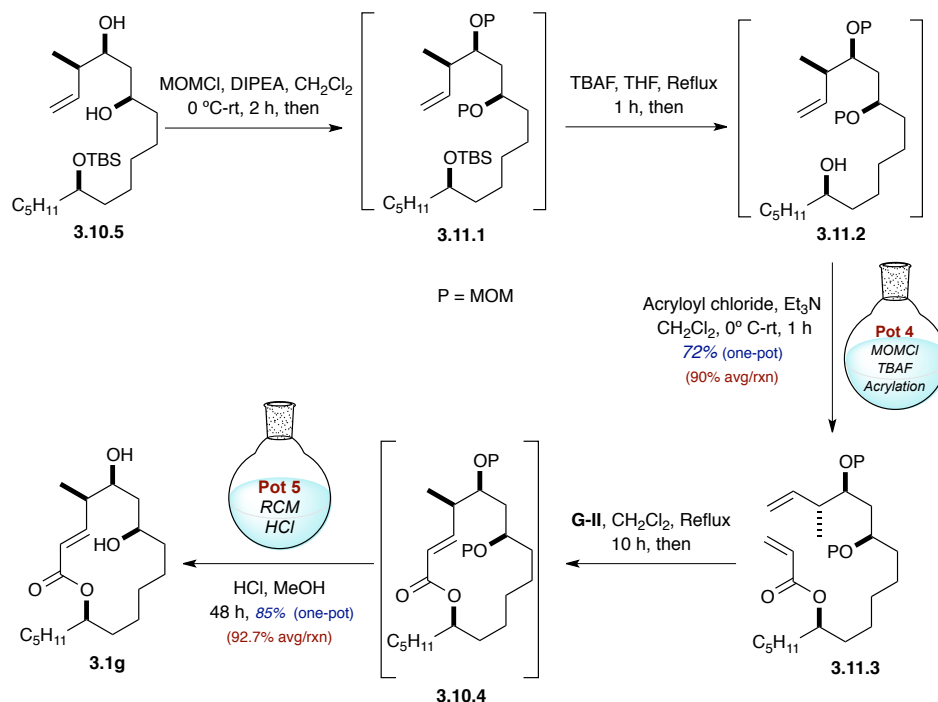
Al[®], which afforded the requisite polyol **3.10.5** bearing a stereotetrad in 79% yield over two reactions in two pots with a single chromatographic purification.

Scheme 3.10. *Synthesis of TBS protected diol 3.10.5.*



The TBS-protected diol **3.10.5** was next subjected to a one-pot sequential MOM-protection/TBS-deprotection/acrylation sequence (Scheme 3.11).⁷ To this end, the alcohol **3.10.5** was first subjected to MOM-protection using MOMCl, DIPEA and CH_2Cl_2 . After completion of reaction, the TBS-group was removed using TBAF in refluxing THF for 1 h, which produced the alcohol fragment **3.11.2**. The crude alcohol **3.11.2** was acrylated using Et₃N and acryloyl chloride at 0 °C, which furnished the acrylate fragment **3.11.3** in 72% yield over three reactions in one-pot (90% av/rxn). Finally, a one RCM/MOM-deprotection sequence afforded the macrolactone **3.1g** in 85% yield over two reactions in a single pot (92.7% av/rxn).

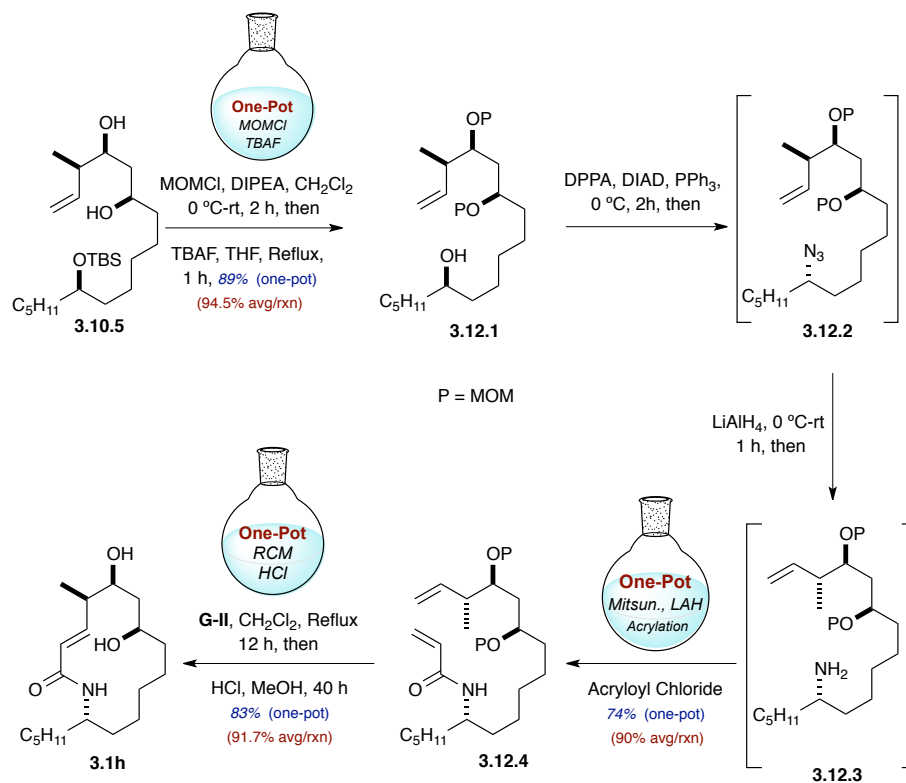
Scheme 3.11. *Synthesis of macrolactone analog 3.1g.*



Accordingly, we were able to accomplish the synthesis of macrolactam analog **3.1h** using three consecutive one-pot sequential operations, starting from TBS-protected alcohol **3.10.5** (Scheme 3.12). Accordingly, a one-pot sequential MOM-protection/TBS-deprotection afforded the MOM-protected alcohol **3.12.1** in excellent yield (89% over two reactions in one-pot 94.5% av/rxn). Next, we carried out a one-pot sequential transformation consisting of a Mitsunobu/reduction/acrylation sequence to furnish the acrylamide **3.12.4** in excellent yield. To this end, the MOM-protected alcohol **3.12.1** was subjected to Mitsunobu reaction using DPPA, DIAD, in THF. After completion of Mitsunobu reaction, the crude azide **3.12.2** was reduced using LiAlH₄ at 0 °C in THF to furnish the amine product **3.12.3** without any solvent change. Acrylation of the crude amine afforded the acrylamide fragment **3.12.4** in 74% yield over three reactions in one-pot (90% av/rxn). In similar fashion as outlined in the synthesis of macrolactone analog

(Scheme 3.11), the diene **3.12.4** was subjected to a final one-pot RCM/MOM-deprotection sequence to accomplish the synthesis of macrolactam analog **3.1h** in good yield over two reactions in one-pot.

Scheme 3.12. Synthesis of macrolactam analog **3.1h** of Sch-725674.

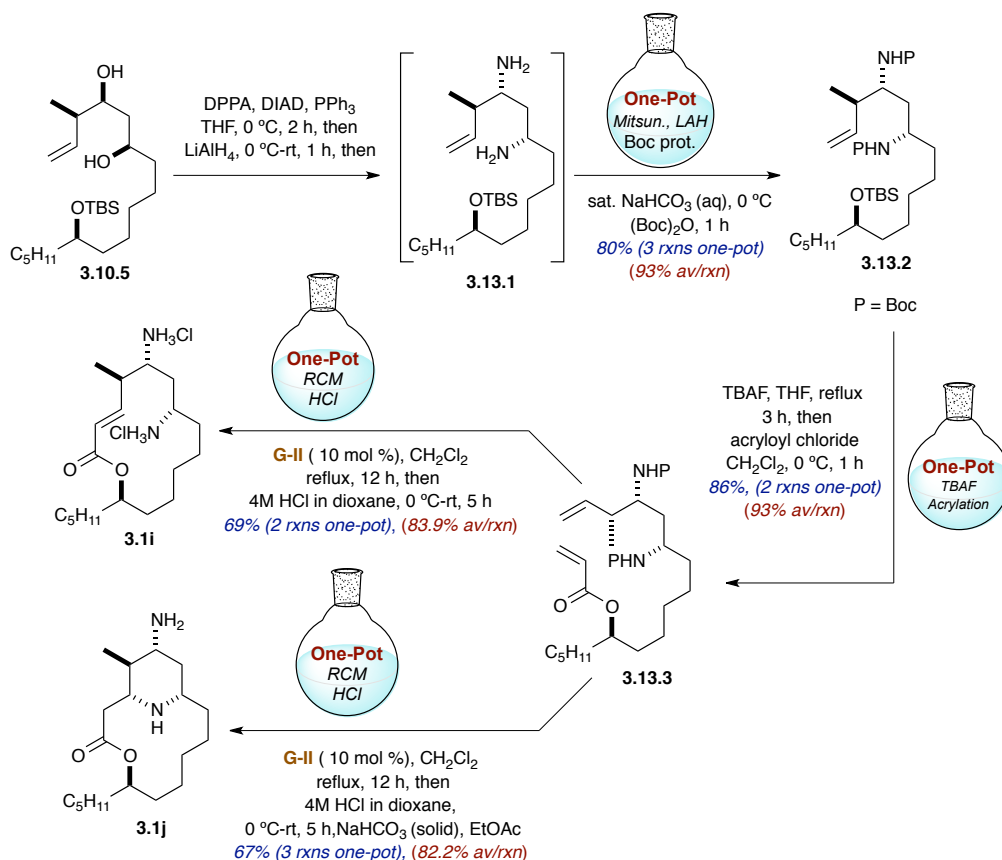


Overall both analogs **3.1g** and **3.1h** of Sch-725674 (**3.1f**) were efficiently synthesized in a pot- and step-economical manner from readily prepared starting materials (**3.3f** and **3.4b**) over five and six pots consisting of a total of ten and twelve reactions, respectively, which significantly reduced the total amount of workup and purification procedures.

3.4.2. Syntheses of amine substituted macrolactone **3.1i** and **3.1j**

For the syntheses of both macrolactone **3.1i** and **3.1j**, the common precursor **3.10.5** was subjected to a consecutive three one-pot sequential processes, which furnished the desired products (**3.1i** and **3.1j**) in efficient and pot-economical manner (Scheme 3.13). Toward this goal, the TBS-protected diol **3.10.5** was subjected to a one-pot sequential Mitsunobu/reduction/Boc-protection sequence to furnish the Boc-protected amine **3.13.2** in 80% yield over three reactions in one-pot (93% av/rxn). A second one-pot two reactions sequence consisting of TBS- deprotection/acrylation enabled the synthesis of acrylate fragment **3.13.3** in excellent yield over two reactions.

Scheme 3.13. Synthesis of amine substituted macrolactone **3.1i** and **3.1j** analogs.

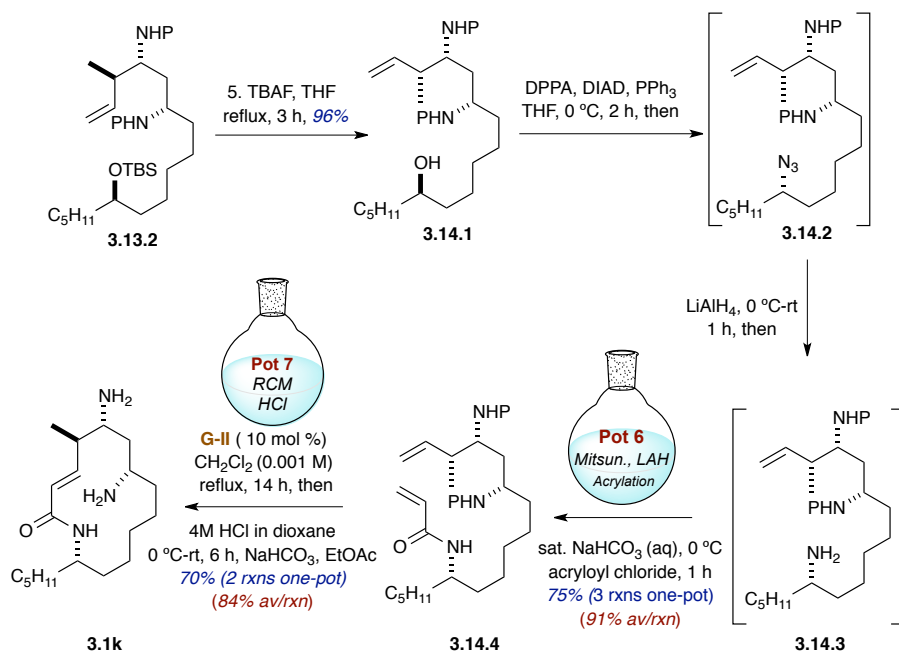


Next, we carried out a third consecutive one-pot sequential RCM/Boc deprotection sequence, which afforded the macrolactone analog **3.1i** in 69% yield over two reactions. The corresponding macrolactone analog **3.1j** was obtained by simply quenching the HCl salt of amine substituted macrolactone **3.1i** with NaHCO₃ to afford the Michael addition product **3.1j** in 67% yield for the three reactions in one-pot. Both the amine substituted macrolactone analogs **3.1i** and **3.1j** were efficiently synthesized starting from readily prepared (*S,S*)-triene, **3.3f** and CM partner **3.4b** in a sequence of six pots consisting of a total of twelve and thirteen reactions, respectively.

3.4.3. Synthesis of amine substituted macrolactam **3.1k**

In similar fashion, the amine substituted macrolactam analog **3.1k** was synthesized in three pots consisting a total of six reactions starting from Boc-protected amine **3.13.2** (Scheme 3.14). Toward this goal, the TBS-deprotection of **3.13.2** afforded the alcohol **3.14.1** in excellent yield.

Scheme 3.14 Synthesis of macrolactam analog **3.1k** of Sch-725674.



Subsequently, a one-pot Mitsunobu/reduction/acrylation sequence produced the acrylamide **3.14.4** in 75% yield over three reactions in one pot. Finally, the acrylamide **3.14.4** was converted to the corresponding macrolactam **3.1k** via a one-pot RCM/Boc deprotection in 70% yield for two reactions in a single pot. Overall, we were able to accomplish the asymmetric synthesis of amine substituted macrolactam analog **3.1k** of Sch-725674 from readily prepared (*S,S*)-triene **3.3f** and CM partner **3.4b** in 7 pots consisting a total of thirteen reactions.

3.5. Conclusion

In summary, we were able to accomplish the asymmetric synthesis of structurally diverse analogs of Sch-725674 in a rapid, efficient, pot-economical and library amenable manner. In this regard, five different Sch-analogs **3.1g–3.1k** were synthesized via a sequence of 5-to-7 consecutive one-pot sequential operations consisting of a total of 10–13 reactions with only 5-to-7 workup/purification procedures. All final compounds have been submitted for biological evaluations (antifungal and antibacterial activities) to our collaborators.

3.6. Special Acknowledgment

The author acknowledges that portions of this chapter, including the preliminary Introduction and Results and Discussion sections, are reprinted, in part, or adapted from the following publications, with permission from the corresponding publishers:

Bodugam, M.,[‡] Javed, S.,[‡] Ganguly, A.; Torres, J.; Hanson, P. R. A Pot-Economical Approach to the Total Synthesis of Sch-725674. *Org. Lett.* **2016**, *18*, 516–519 (‡ Equal contribution).

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Chapter-4

Efforts Towards the Asymmetric Total Synthesis of
(-)-13-Desmethyl-lyngbouilloside, an Unnatural Analog of
Lyngbouilloside

4.1. Introduction

Bioactive natural products and corresponding analogs with unique structural features have long been a center of attention for organic chemists. In particular, marine macrolide glycosides¹ with cytotoxic, antibacterial,² antifungal and antiviral³ activities have inspired many successful total syntheses. (–)-Lyngbouilloside (**4.1**)⁴ and (–)-lyngbyalloside B (**4.1d**)⁵ are closely related cytotoxic 14-membered macrolides, which were isolated in 2002 from two different marine cyanobacteria of the genus *lyngbya* *bouillonii* (*Oscillatoriaceae*) (Figure 4.1). Initial biological screening demonstrated that **4.1a** and **4.1d** exhibit modest cytotoxic activity against neuroblastoma and KB cells with IC₅₀ values of 17 μ M and 4.3 μ M, respectively.⁶ Motivated by the biological activity and unique structural features of both (–)-lyngbouilloside (**4.1a**) and (–)-lyngbyalloside B (**4.1d**), a number of partial and total syntheses of **4.1a** and **4.1d** have been reported in the literature.⁷

In 2013, Fuwa and coworkers reported the total synthesis of (–)-13-desmethyl-lyngbyalloside B (**4.1f**) as part of their ongoing program towards the total synthesis of lyngbyalloside B (**4.1d**) (Figure 4.1).^{7d} Later, in 2015, they accomplished the total synthesis of (–)-lyngbyalloside B (**4.1d**).^{7e} Based on spectroscopic analysis, the authors reported that the previously assigned stereochemical configuration of **4.1d** was incorrect. The authors, therefore, reassigned the stereochemical configuration of (–)-lyngbyalloside B (**4.1d**) and resynthesized (–)-lyngbyalloside B (**4.1e**) with the corrected stereochemical configuration (Figure 4.1). After completion of the total synthesis of **4.1e**, Fuwa and coworkers evaluated the anti-proliferative activity of **4.1d**, **4.1e**, **4.1f** and (–)-lyngbyalloside B aglycon against human cancer cells lines and found good inhibition

potencies against the proliferation of HL-60 cells.^{7e} These biological results revealed some important implications for understanding the structural activity relationship of (–)-lyngbyaloside B and its unnatural analogs including; (i) the presence of 3,4-di-*o*-methyl-L-rhamnopyranoside moiety is essential for anti-proliferative activity against the tested cell lines, (ii) analysis of stereochemical configuration at the C10/C11 position in **4.1d** and **4.1e** had no effect on the anti-proliferative activity, and (iii) (–)-13-desmethyl-lyngbyaloside B (**4.1f**) displayed more potent anti-proliferative activity against all tested cell lines compared to **4.1d** and **4.1e**.

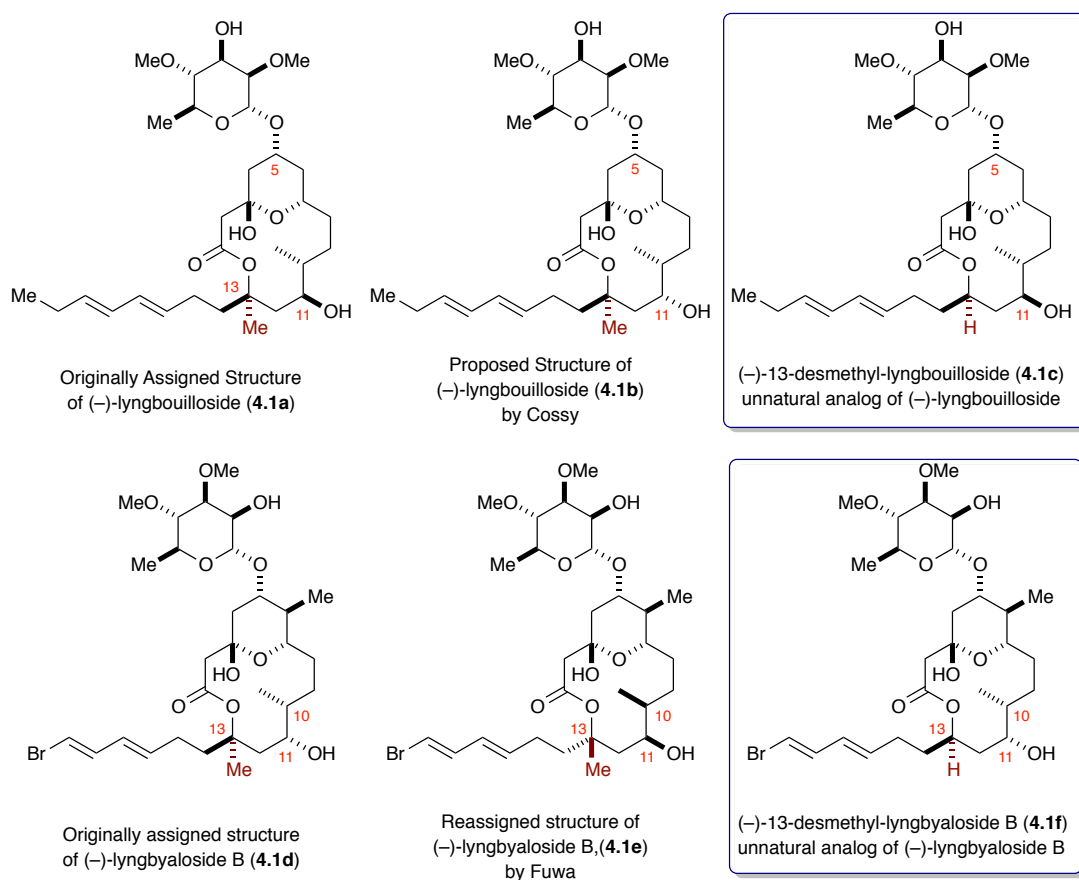


Figure 4.1. (–)-lyngbouilloside (**4.1a**), and (–)-lyngbyaloside B (**4.1e**) and their corresponding unnatural analogs.

This revelation is of prime importance since the omission of the methyl substituent at the C13 position of (–)-lyngbyaloside B (**4.1d**) not only provides

compounds with enhanced anti-proliferative activity against HL-60 cells, but also significantly simplifies the synthesis (32 steps for **4.1d**; 22 steps for **4.1f**, Figure 4.1). Motivated by these intriguing results and aligned with our ongoing efforts toward the total synthesis of (–)-lyngbouilloside (**4.1a**), we were interested in the asymmetric synthesis and biological evaluation of (–)-13-desmethyl-lyngbouilloside (**4.1c**) and corresponding analogs (Figure 4.1). This chapter will describe a brief history of the previously reported total syntheses of (–)-lyngbouilloside (**4.1a**), (–)-lyngbyalloside B (**4.1d**) and the ongoing efforts towards the asymmetric total synthesis of (–)-13-desmethyl-lyngbouilloside (**4.1c**).

4.2. Overview of previous efforts toward the syntheses of (–)-lyngbouilloside (4.1a**)**

In 2002, Gerwick and coworkers isolated and structurally characterized a novel cytotoxic macrolide, (–)-lyngbouilloside (**4.1a**), from cyanobacteria *lyngbya bouillonii*. (–)-Lyngbouilloside display modest cytotoxic activity against neuroblastoma cells with an IC₅₀ value of 17 μ M.⁴ Based on spectroscopic analysis and chemical derivatization, the structure of **4.1a** was identified as a glycosylated 14-membered macrolide (Figure 4.1) containing a six-membered cyclic hemiketal, an (*E,E*)-configured octadienyl side chain, and an L-rhamnose-derived pyranoside ring at the C5 position of the macrolactone ring. Thus far, there is no literature report of the total synthesis of (–)-lyngbouilloside (**4.1a**). However, there are a number of reports of the partial syntheses of **4.1a**.

4.2.1. Stereoselective synthesis of the C1–C13 fragment of (–)-lyngbouilloside

In 2008, Cossy and coworkers reported the first stereoselective synthesis of the fully functionalized carbon backbone **4.2a** of (–)-lyngbouilloside using a pivotal cross-metathesis (CM) reaction between fragments **4.2b** and **4.2c** (Figure 4.2).^{7a} The authors

envisioned a retrosynthetic approach for the C9–C13 fragment **4.2b** that could be synthesized from commercially available (*S*)-citramalic acid (**4.2d**) whereas the C1–C8 fragment **4.2c** could be accessed from commercially available 4-pentenal (**4.2e**).

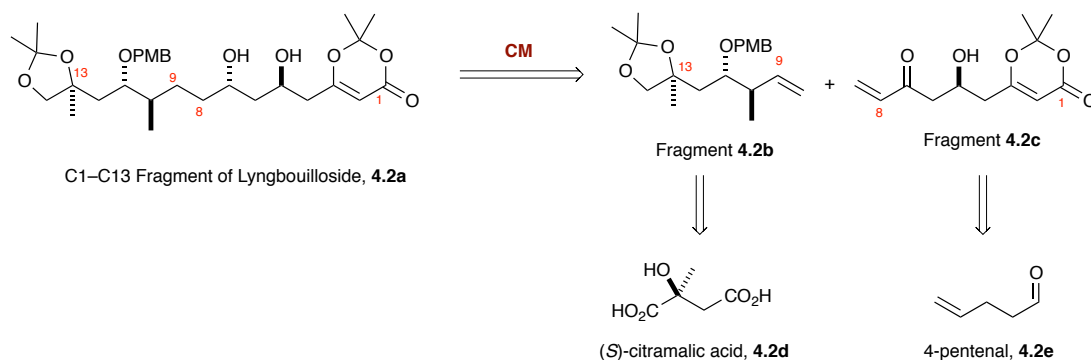


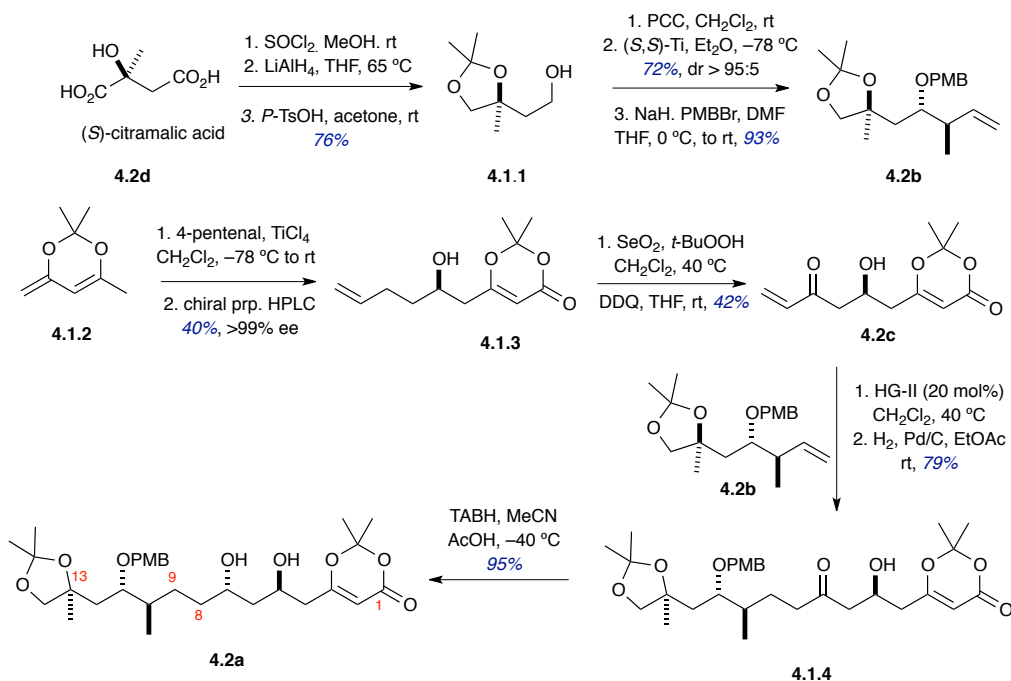
Figure 4.2. Retrosynthetic analysis of the C1–C13 fragment of (–)-lyngbouilloside (**4.1a**).

The forward synthesis of the subunit **4.2b** commenced with esterification of (*S*)-citramalic acid (**4.2d**) followed by reduction of the resulting dimethyl citramalate, to access the corresponding 1,2-diol (Scheme 4.1). Subsequent selective protection as an acetonide using acetone and PTSA provided the known acetal fragment **4.1.1** in 76%, overall yield. The acetal fragment was oxidized to the aldehyde using PCC, which was converted to the corresponding homoallylic alcohol with high diastereoselectivity (dr > 95:5) using a face-selective crotyltitanium complex (*S,S*)-**Ti**⁸ (72% over all yield). The resulting alcohol was protected as PMB ether, affording the CM partner **4.2b** in 93% yield.

The synthesis of fragment **4.2c** began with an aldol reaction of **4.1.2** with commercially available 4-pentenal to furnish the alcohol **4.1.3**. Allylic oxidation was performed using SeO₂ and *t*-BuOOH to access the required enone fragment **4.2c**. With both desired fragments (**4.2b** and **4.2c**) in hand, a cross-metathesis reaction was performed using **HG-II**⁹ catalyst followed by directed catalytic hydrogenation of the

olefin in the enone fragment using H₂ on Pd/C to afford the fully functionalized backbone of (–)-lyngbouilloside (**4.1a**). Finally, reduction of the ketone moiety in fragment **4.1.4** using Me₄N(OAc)₃BH (TABH) furnished the C1–C13 fragment in excellent yield. Overall, the synthesis of fully functionalized C1–C13 fragment **4.2a** of (–)-lyngbouilloside was achieved in nine steps with 38% overall yield starting from commercially available (*S*)-citramalic acid (**4.2d**).

Scheme 4.1. Synthesis of fragments **4.2b** and **4.2c** and completion of fully functionalized C1–C13 fragment **4.2c** of (–)-lyngbouilloside (**4.1a**).



4.2.2. Enantioselective synthesis of the lyngbouilloside macrolactone core

In 2009, Ley and coworkers reported an enantioselective synthesis of the macrolactone core **4.3b** of (–)-lyngbouilloside (**4.1a**) (Figure 4.3).^{7b} The key reactions involved in the synthesis of **4.3b** were enolate-lactone coupling and a late-stage RCM/hydrogenation sequence that furnished the macrolactone core of **4.1a** in a convergent manner. On the basis of ¹H NMR and ¹³C NMR analysis and DFT-based

NMR chemical shift calculations, the authors proposed that the stereochemical assignment at the C11 position of (–)-lyngbouilloside (**4.1a**) might be incorrect.

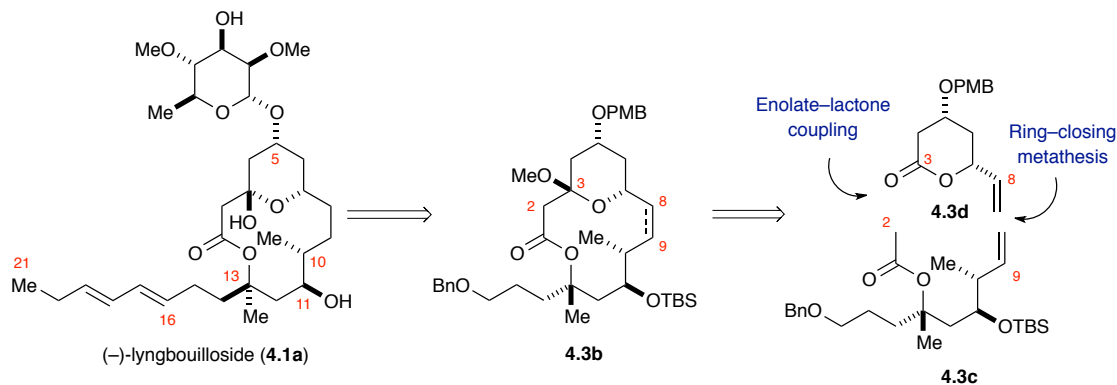
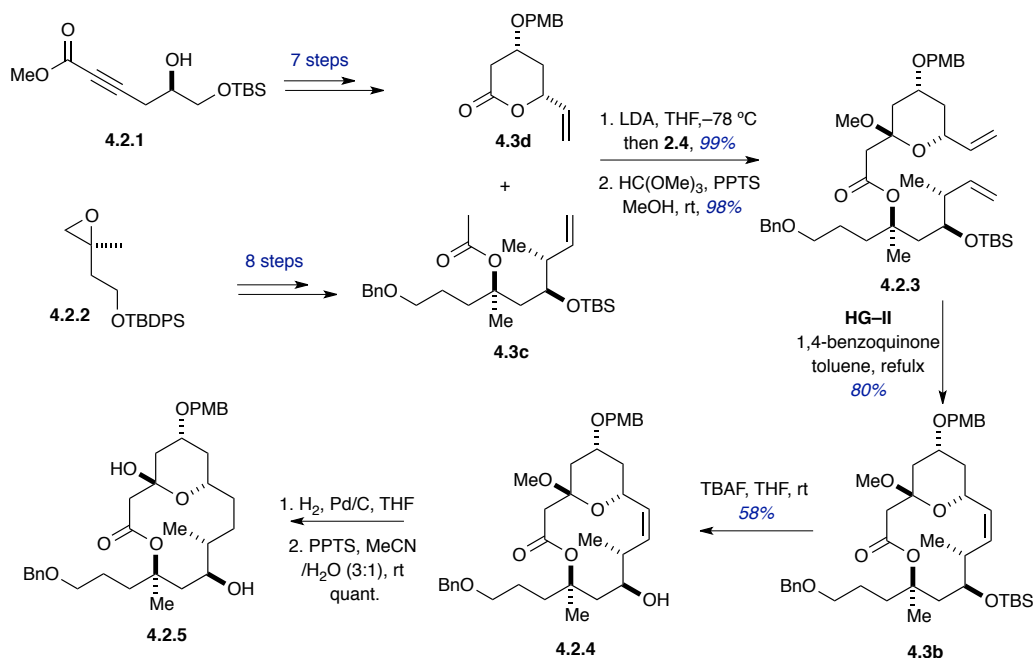


Figure 4.3. Retrosynthetic analysis of macrolactone core **4.3b** of (–)-lyngbouilloside (**4.1a**).

The required lactone **4.3d** and ester **4.3c** fragments for the construction of macrolactone **4.3b** were synthesized from the corresponding known ynone **4.2.1**¹⁰ and epoxide **4.2.2**¹¹ in seven and eight steps, respectively (Scheme 4.2). The lactone **4.3d** was treated with two equivalents of the lithium enolate of **4.3c** to afford the corresponding lactol in quantitative yield, which was subsequently converted to the acetal fragment **4.2.3** in 98% yield. After extensive model reaction studies, the diene fragment **4.2.3** was successfully cyclized to the macrolactone fragment **4.3b** utilizing the **HG-II** catalyst. The macrolactone was next subjected to TBS-deprotection using TBAF, followed by hydrogenation of the resulting C=C double bond using H₂, Pd/C, and demethylation using PPTS, to provide the fully functionalized macrolactone core **4.2.5** of (–)-lyngbouilloside (**4.1a**).

Scheme 4.2. Convergent synthesis of macrolactone core **4.2.4** of lyngbouilloside.



4.2.3. Asymmetric total synthesis of (–)-lyngbouilloside aglycon

In 2012, Cossy and coworkers reported the first enantioselective total synthesis of (–)-lyngbouilloside aglycon **4.4a** according to the originally assigned structure (Figure 4.4). The authors utilized a pivotal acylketene macrolactonization of a tertiary methyl carbinol (C13 in **4.4a**)^{7c} to circumvent fundamental issues associated with macrolactonization of sterically encumbered alcohols. Based on spectroscopic analysis, the authors proposed a revised structure of (–)-lyngbouilloside (**4.1b**) with a stereochemical reassignment of the C11 stereogenic center. The authors proposed that lyngbouilloside aglycon **4.4a** could be assembled via macrolactonization of the 1,3-*anti*-diol fragment **4.4b**, which in turn can be synthesized from β-hydroxyenone **4.4c** (Figure 4.4). The synthesis of β-hydroxyenone **4.4c** was planned from the two key fragments

4.4d and **4.4e** via a CM reaction. Both **4.4d** and **4.4e** could be readily prepared from commercially available 3-methylbut-3-enol (**4.4f**) and 4-pentenal (**4.4g**), respectively.

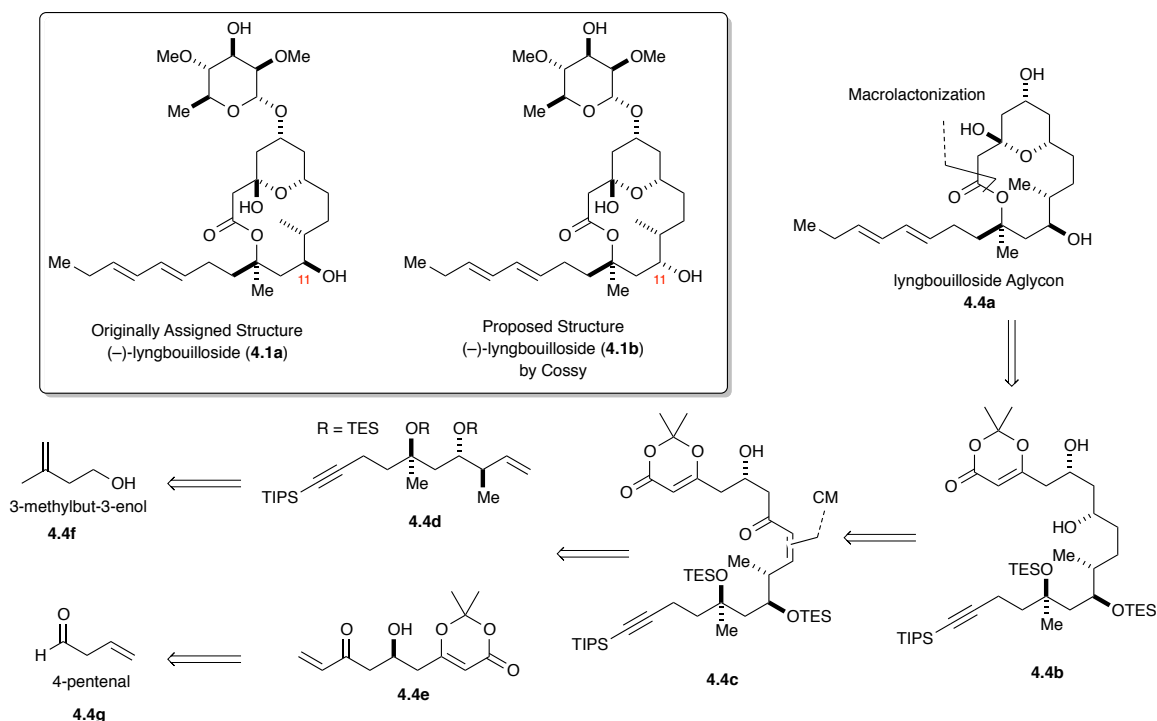
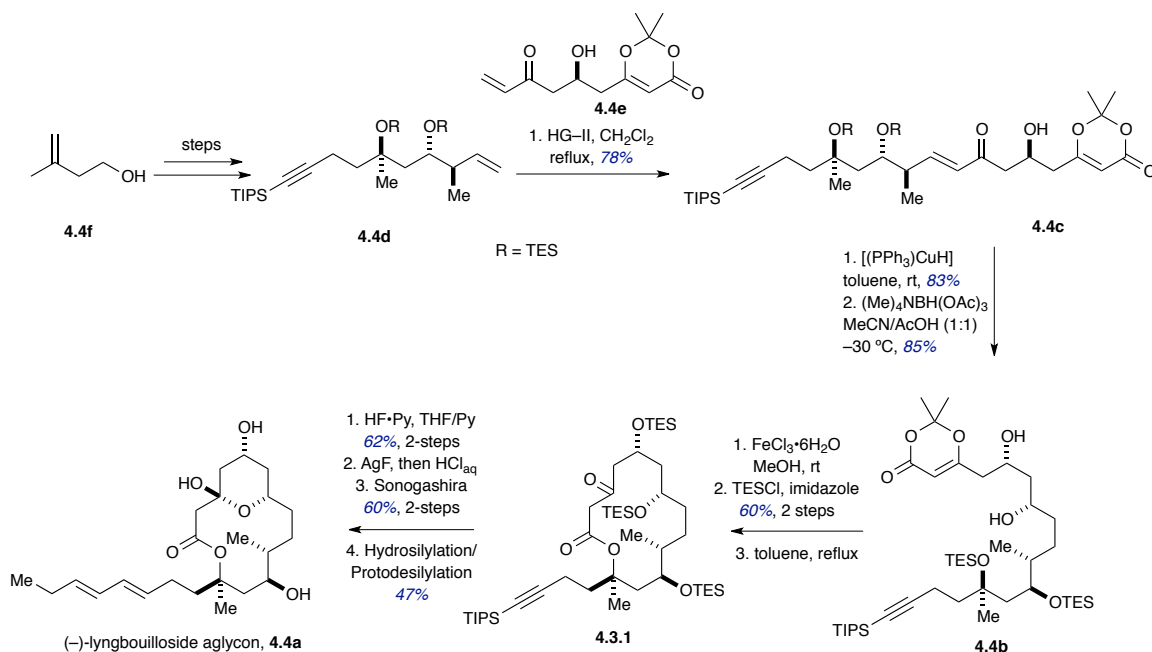


Figure 4.4. Retrosynthetic analysis of lyngbouilloside aglycon **4.4a**.

The forward synthesis of lyngbouilloside aglycon commenced with the synthesis of the CM partner **4.4d** (Scheme 4.3), which was completed in nine steps starting from commercially available 3-methylbut-3-enol (**4.4f**). Cross metathesis reaction between diol fragment **4.4d** and previously reported enantiopure dioxinone fragment **4.4e**^{7a} using the **HG-II** catalyst, afforded the enone fragment **4.4c** in 78% yield with excellent *E*-selectivity (*E/Z* > 95:5). Conjugate reduction of the enone fragment **4.4c**, using Stryker's reagent,¹² afforded the β -hydroxy ketone, which was subsequently subjected to the Evans TABH-mediated 1,3-*anti* reduction.¹³ This two-step sequence afforded 1,3-*anti* diol fragment **4.4b** in 71% overall yield with excellent diastereoselectivity (dr >95:5). Next, the authors removed the TES group using $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ in methanol,¹⁴ and subsequently,

the three secondary alcohols were selectively reprotected utilizing TESCl and imidazole, which provided the macrocyclization precursor in 60% yield over two steps.

Scheme 4.3. Total synthesis of (–)-lyngbouilloside aglycon



The 14-membered macrolactone core was efficiently assembled via thermolysis of the corresponding dioxinone under rigorous anhydrous conditions, whereby the resulting acylketene intermediate was trapped with free quaternary alcohol to provide the macrolactone core **4.3.1**. TES-deprotection with THF•Py resulted in the simultaneous formation of the pyran ring, followed by TIPS-group removal using AgF•py, which furnished the terminal alkyne. A Sonogashira coupling reaction of the terminal alkyne in **4.3.1** enabled the installation of the side chain, followed by a one-pot hydrosilylation/protodesilylation completed the synthesis of (–)-lyngbouilloside aglycon **4.4a** in 18% over the last four steps. In summary, Cossy and coworkers completed the asymmetric total synthesis of lyngbouilloside aglycon **4.4a** in 20 steps with 2.1% overall yield starting from commercially available 3-methylbut-3-enol (**4.4f**).

4.2.4. Phosphate tether-mediated synthesis of macrolactone core of (–)-lyngbouilloside

In 2015, the Hanson group reported a concise synthesis of the macrolactone core **4.5a**, based on the originally assigned structure of (–)-lyngbouilloside (**4.1a**) (Figure 4.5).^{7g} The key reactions involved in the synthesis of macrolactone core **4.5a** were phosphate tether-mediated one-pot sequential RCM/CM/chemoselective hydrogenation,¹⁵ Roskamp homologation,¹⁶ and Boeckman acylketene cyclization.¹⁷ Retrosynthetic analysis revealed that the macrolactone core **4.5a** could be generated from β -ketoester **4.5b** via a Boeckman acylketene cyclization (Figure 4.5). The β -ketoester **4.5b** in turn could be accessed via oxidative cleavage of the terminal olefin in **4.5c**, followed by a two-carbon Roskamp homologation of the resulting aldehyde.

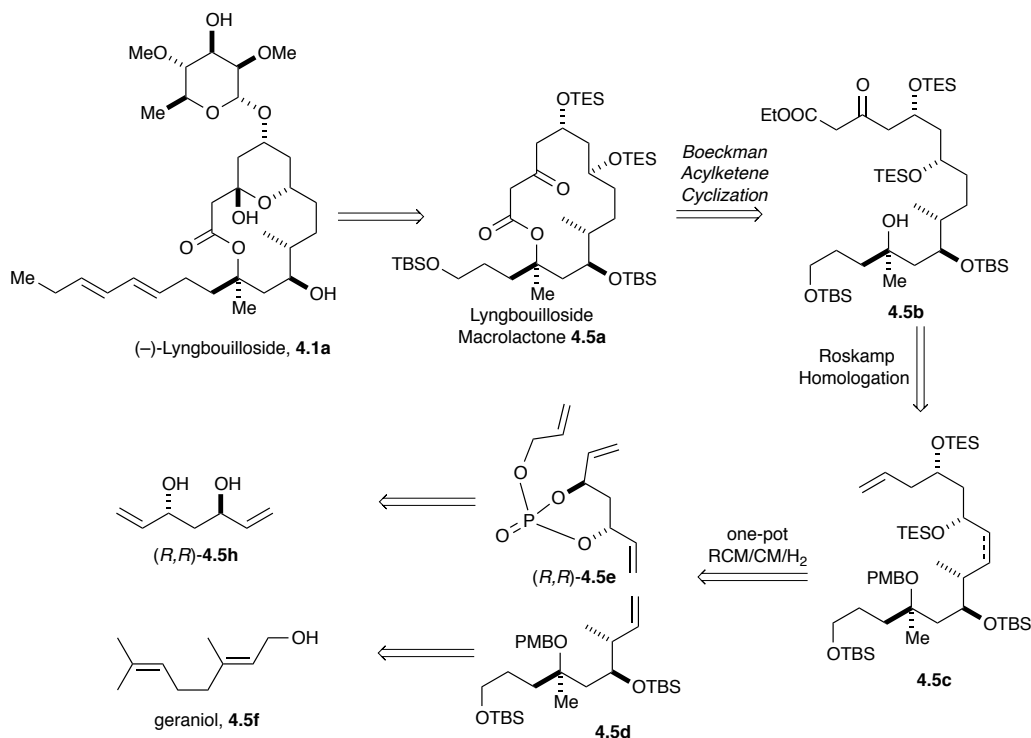
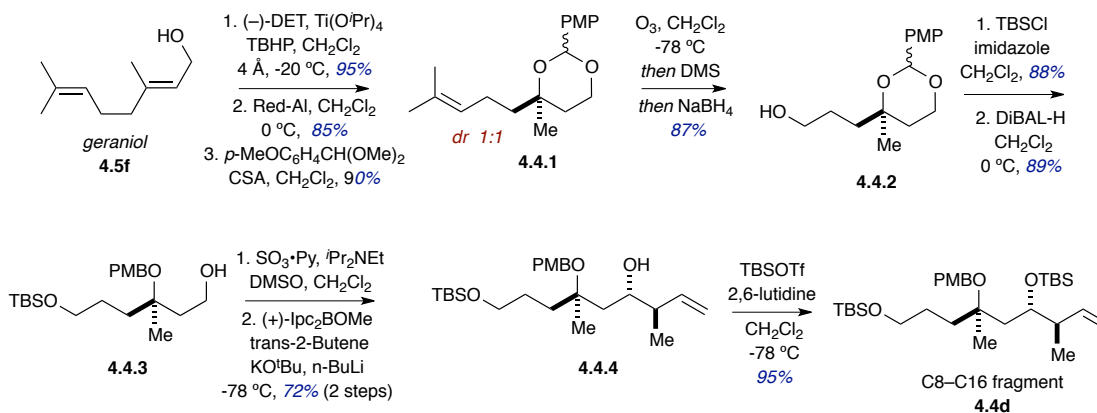


Figure 4.5. Retrosynthetic analysis of macrolactone core **4.5a** of lyngbouilloside (**4.1a**).

The alkene fragment **4.5c** could be obtained via a phosphate tether-mediated one-pot, sequential RCM/CM/chemoselective hydrogenation of (*R,R*)-triene **4.5e**¹⁸ and CM partner **4.5d**. The key fragment **4.5d** could be generated in nine steps from commercially available geraniol (**4.5f**) involving Brown *anti*-crotylation and Sharpless asymmetric epoxidation as key reactions.

The forward synthesis of macrolactone core **4.5a** commenced with the synthesis of the C8–C16 fragment **4.5d** (Scheme 4.4). The commercially available geraniol (**4.5f**) was subjected to Sharpless asymmetric epoxidation¹⁹ followed by regioselective opening of the resulting epoxide using Red-Al, afforded the 1,3-diol fragment in 85% yield.²⁰ The resulting 1,3-diol was subsequently protected as PMP-acetal **4.4.1** with 1:1 diastereoselectivity. Next, the authors subjected the olefin **4.4.1** to ozonolysis, and the resulting aldehyde was reduced to the corresponding primary alcohol **4.4.2** via an *in situ* reductive workup. TBS-protection of the primary alcohol in **4.4.2** followed by regioselective opening of the PMP-acetal ring using DIBAL furnished the alcohol fragment **4.4.3** in excellent yield.

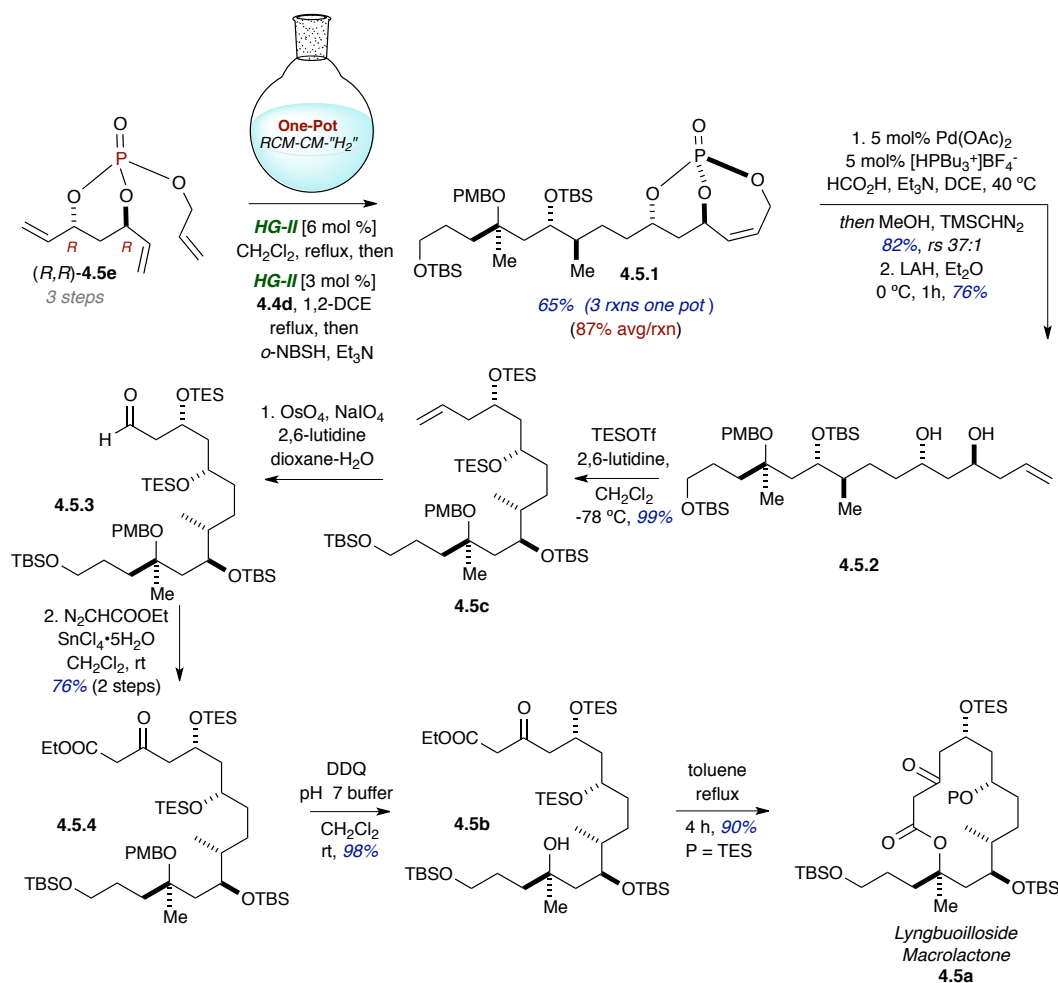
Scheme 4.4. Synthesis of C8–C16 fragment from geraniol (**4.5f**).



Primary alcohol **4.4.3** was subjected to Parikh-Doering oxidation²¹ followed by asymmetric Brown *anti*-crotylation,²² which afforded the required homoallylic alcohol **4.4.4** in 72% yield over two steps. The authors performed TBS-protection of the secondary alcohol in **4.4.4** to complete the synthesis of the requisite C8–C16 CM partner **4.4d** in excellent yield.

With the CM partner **4.4d** in hand, the Hanson and coworkers performed a phosphate tether-mediated one-pot sequential RCM/CM/chemoselective hydrogenation to couple (*R,R*)-triene-**4.5e** with CM partner **4.4d** (Scheme 4.5). This one-pot three-reaction protocol afforded the bicyclic phosphate **4.5.1** in 65% overall yield (87% av/rxn).

Scheme 4.5. Synthesis of lyngbouilloside macrolactone **4.5a**.



Regioselective opening of bicyclic phosphate **4.5.1** via Pd-catalyzed reductive allylic transposition, followed by methylation using TMSCHN₂ in MeOH, afforded the monocyclic phosphate ester in excellent overall yield (82%). The phosphate tether was removed using LiAlH₄ to furnish 1,3-*anti*-diol fragment **4.5.2** as a single diastereomer in good yield. The free alcohols in 1,3-*anti*-diol fragment **4.5.2** were protected with TESOTf (2,6-lutidine, CH₂Cl₂) to generate TES-protected alcohol **4.5c** in quantitative yield. The olefin **4.5c** was subjected to oxidative cleavage employing a modified Johnson-Lemieux protocol developed by Jin and coworkers²³ to afford the corresponding aldehyde **4.5.3**. The crude aldehyde, without further purification, was subjected to Roskamp homologation¹⁶ to provide β -keto ester **4.5.4** in 76% yield over two steps with only one purification procedure. Next, PMB-ether was deprotected using DDQ to generate alcohol **4.5b** in 98% yield. Boeckman acylketene cyclization¹⁷ of the resulting alcohol in refluxing toluene (0.0007 M) afforded the macrolactone core **4.5a** of (–)-lyngbouilloside (**4.1a**) in good yield (90%).

4.3. Isolation, biological activity and total synthesis of (–)-lyngbyaloside B (4.1d**) reported by the Fuwa group**

In 2002, the Moore group isolated a structurally similar 14-membered macrolide (–)-lyngbyaloside B (**4.1d**) from cyanobacterium *Lyngbya* sp. (Figure 1).⁵ Initial biological screening demonstrated that (–)-lyngbyaloside B exhibited moderate cytotoxic activity against KB cells with IC₅₀ values of 4.3 μ M. The structure and relative stereochemical configuration of **4.1d** were proposed based on extensive 2D-NMR studies and ROESY correlations. However, the absolute stereochemistry of (–)-lyngbyaloside B (**4.1d**) remained unknown due to the scarce availability of the authentic natural source.

4.3.1. Total synthesis of (–)-13-desmethyl-lyngbyaloside B

In 2013, Fuwa and coworkers reported the synthesis of (–)-13-desmethyl-lyngbyaloside B (**4.1f**), an unnatural analog of (–)-lyngbyaloside B (**4.1d**) (Figure 4.6).^{7d} Upon retrosynthetic analysis of (–)-13-desmethyl-lyngbyaloside B (**4.1f**), the authors envisioned that **4.1f** could be assembled from the corresponding macrolactone **4.6a** via glycosylation²⁴ and a Stille-type reaction,²⁵ which install the L-rhamnose-derived pyranoside ring **4.6b** at the C5 position of the macrolactone core and the bromodiene side chain **4.6c**, respectively. The macrolactone core **4.6a** could be constructed through a convergent manner from alcohol **4.6d** and carboxylic acid **4.6e** using Yamaguchi reaction conditions followed by RCM reaction.

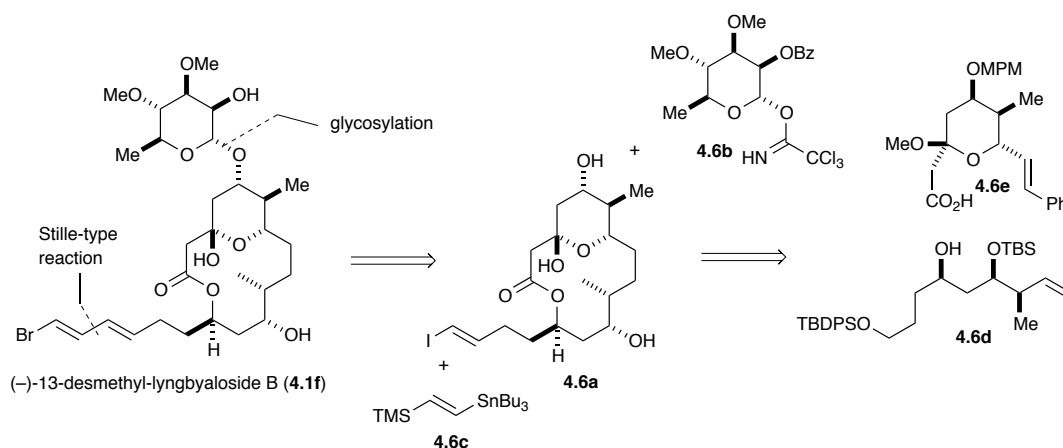
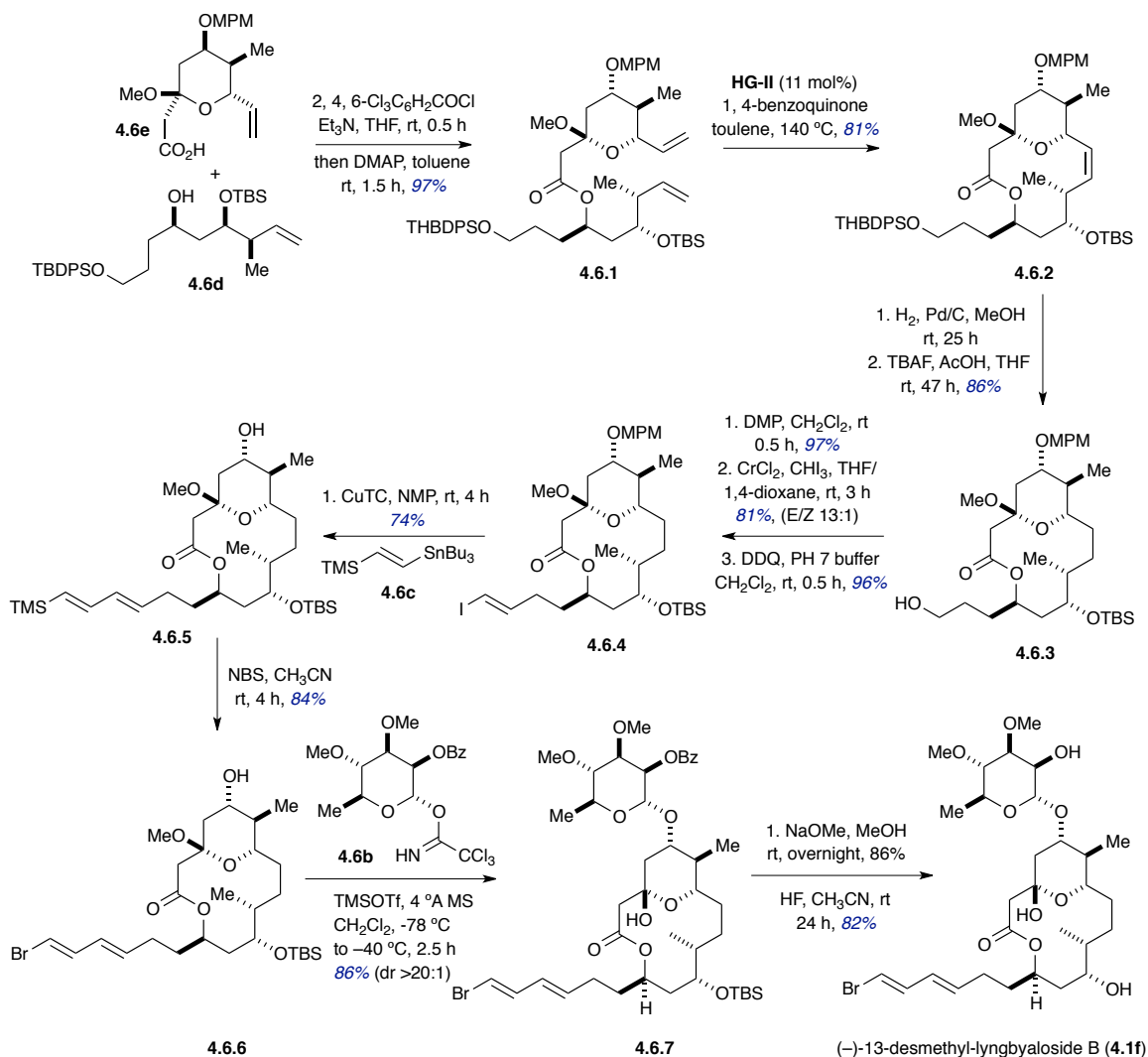


Figure 4.6. Retrosynthetic analysis of (–)-13-desmethyl-lyngbyaloside B (**4.1f**).

The required alcohol fragment **4.6d** and carboxylic acid **4.6e** were synthesized in seven and nine steps, respectively, from a known homoallylic alcohol²⁶ and a TES-protected alcohol (Scheme 4.6).²⁷ The diene fragment **4.6.1** was assembled in quantitative yield from the corresponding carboxylic acid **4.6e** and alcohol fragments **4.6d** via esterification reaction.²⁸ Ring-closing metathesis of the diene **4.6.1** using the **HG-II** catalyst (11 mol%) afforded the macrolactone **4.6.2** in 81% yield. Hydrogenation of the

resulting C–C double bond, and selective deprotection of TBDPS with TBAF, furnished the alcohol **4.6.3** in 86% yield over 2 steps.

Scheme 4.6. Total synthesis of (–)-13-desmethyl-lyngbyaloside B (**4.1f**).



Oxidation of the primary alcohol in **4.6.3** followed by Takai olefination²⁹ of the resulting aldehyde and MPM deprotection furnished the (*E*)-vinyl iodide **4.6.4** in good yield. The resulting (*E*)-vinyl iodide was subsequently coupled with vinyl stannane **4.6c**³⁰ via Stille type reaction to afford the vinyl silane **4.6.5** in 74% yield. Bromodesilylation³¹ of **4.6.5** furnished the aglycon **4.6.6** in 84% yield. Next, the authors performed a

glycosylation reaction to introduce the L-rhamnopyranose ring stereoselectively at C5 position of the macrolactone core by treating the aglycon **4.6.6** with trichloroacetimidate **4.6b**. Finally, global deprotection led to the completion of **4.1f**. Taken collectively, starting from the known homoallylic alcohol²⁶ the synthesis of (–)-13-desmethyl-lyngbyalose B (**4.1f**) was completed in 7% overall yield in a route having an LLS of 20 steps.

4.3.2. Total synthesis and biological evaluation of (–)-lyngbyalose B and its analogs

In 2015, Fuwa and coworkers reported the first total synthesis, stereochemical reassignment, and biological evaluation of (–)-lyngbyalose B (**4.1d**).^{7e} Retrosynthetically, the authors planned a late-stage introduction of glycoside ring **4.7b** and bromodiene side chain via glycosylation²⁴ and Stille-type reaction,²⁵ respectively (Figure 4.7). The macrolactone core **4.7a** was envisaged via macrocyclization of acylketene generated from the corresponding dioxinone fragment **4.7c**.

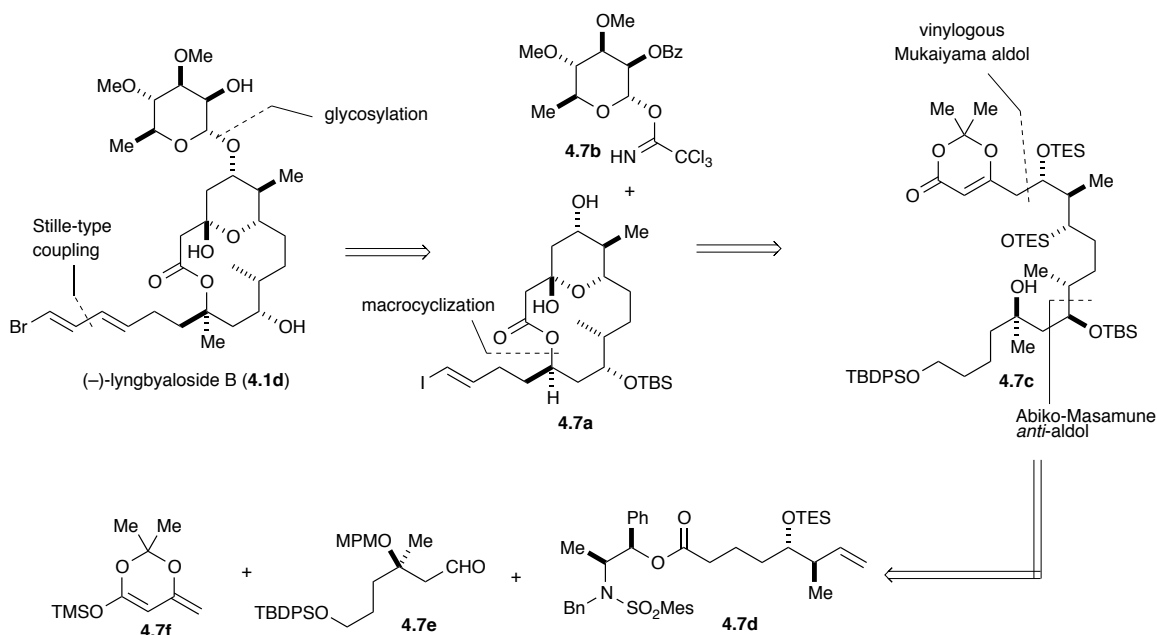


Figure 4.7. Retrosynthetic analysis of (–)-lyngbyalose B.

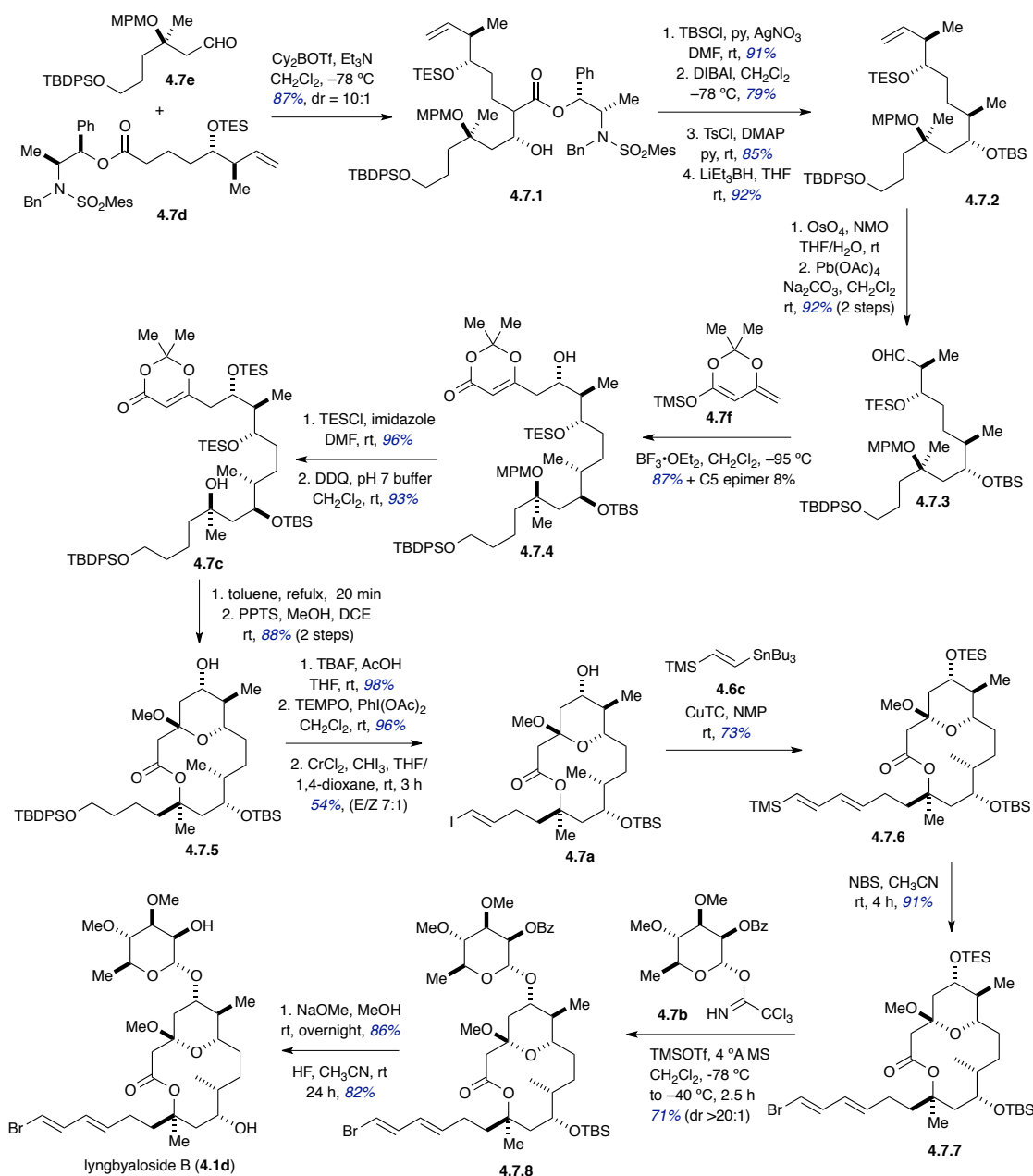
The dioxinone fragment was planned in a convergent manner from the olefin fragment **4.7d**, aldehyde **4.7e** and a known silyl dienol ether **4.7f** using a Abiko–Masamune *anti*-aldol reaction,³² followed by a vinylogous Mukaiyama aldol reaction.³³

The forward synthesis of (–)-lyngbyaloside B (**4.1d**) began with the synthesis of olefin fragment **4.7d** and aldehyde fragment **4.7e** (Scheme 4.7). Both **4.7d** and **4.7e** were synthesized from the corresponding known aldehyde³⁴ and ester³⁵ fragments in six and eight steps, respectively. The key building blocks **4.7d** and **4.7e** were subsequently subjected to Abiko–Masamune *anti*-aldol reaction³² to afford the alcohol **4.7.1** in 87% yield (d.r. = 10:1). Silylation of the alcohol **4.7.1** using TBSCl, followed by reductive removal of the ester, provided the primary alcohol in 79% yield. The resulting alcohol was subsequently subjected to tosylation, followed by reduction with LiEt₃BH, furnished olefin **4.7.2** in good yield. Oxidative cleavage of the terminal olefin in **4.7.2** afforded aldehyde **4.7.3** in 92% over two reactions.

A vinylogous Mukaiyama Aldol reaction³³ of aldehyde **4.7.3** provided the dioxinone fragment **4.7.4** in 87% yield. TES-protection of the alcohol in **4.7.4**, followed by MPM-deprotection, afforded the quaternary alcohol **4.7c** in 93% yield. The alcohol was subsequently cyclized to the corresponding macrolactone in refluxing toluene, followed by exposure to acidic conditions (PPTS, MeOH), to provide the methyl acetal **4.7.5** in 88% yield. Selective TBS-deprotection, followed by oxidation of the resulting primary alcohol using TEMPO and PhI(OAc)₂, provided the aldehyde fragment in 96% yield. Takai iodoolefination of the aldehyde afforded the vinyl iodide **4.7a** in 54% yield as an inseparable mixture of *E/Z* isomers (7:1). Next, the authors coupled the vinyl iodide **4.7a** with vinyl stannane **4.6c** through a Stille-type reaction to afford vinyl silane **4.7.6** in

73% yield. Bromodesilylation of vinyl silane, followed by stereoselective glycosylation with trichloroacetimidate **4.7b**, afforded **4.7.8** in 71% yield. Finally, global deprotection using NaOMe and HF provided the natural product (–)-lyngbyaloside B (**4.1d**) in good yield.³⁶

Scheme 4.7 Total synthesis of (–)-lyngbyaloside B (4.1d**).**



Based on spectroscopic analysis, Fuwa and coworkers reported that the previously assigned stereochemical configuration of (–)-lyngbyaloside B (**4.1d**) was incorrect (Figure 4.8).^{7e} Utilizing ¹³C NMR, ¹H NMR and ROESY correlations the authors reassigned the stereochemical configuration at C10/C11 of (–)-lyngbyaloside B (**4.1e**). The authors synthesized (–)-lyngbyaloside B (**4.1e**) from the corresponding *ent*-**4.8a** and **4.8b** in similar fashion as described for **4.1d**.³⁷ The specific rotation value obtained for **4.1e** ($[\alpha]_D^{25} -16.9$ (c 0.20, CHCl₃)) was in close agreement with the authentic natural product ($[\alpha]_D^{25} -20$ (c 0.10, CHCl₃)). After resynthesizing (–)-lyngbyaloside B (**4.1e**) the authors tested the natural product (–)-lyngbyaloside B (**4.1e**) and its unnatural analogs (**4.1d**, **4.8b** and **4.5a**) against human cancer cells lines and found good inhibition potencies against the proliferation of HL-60 cells.

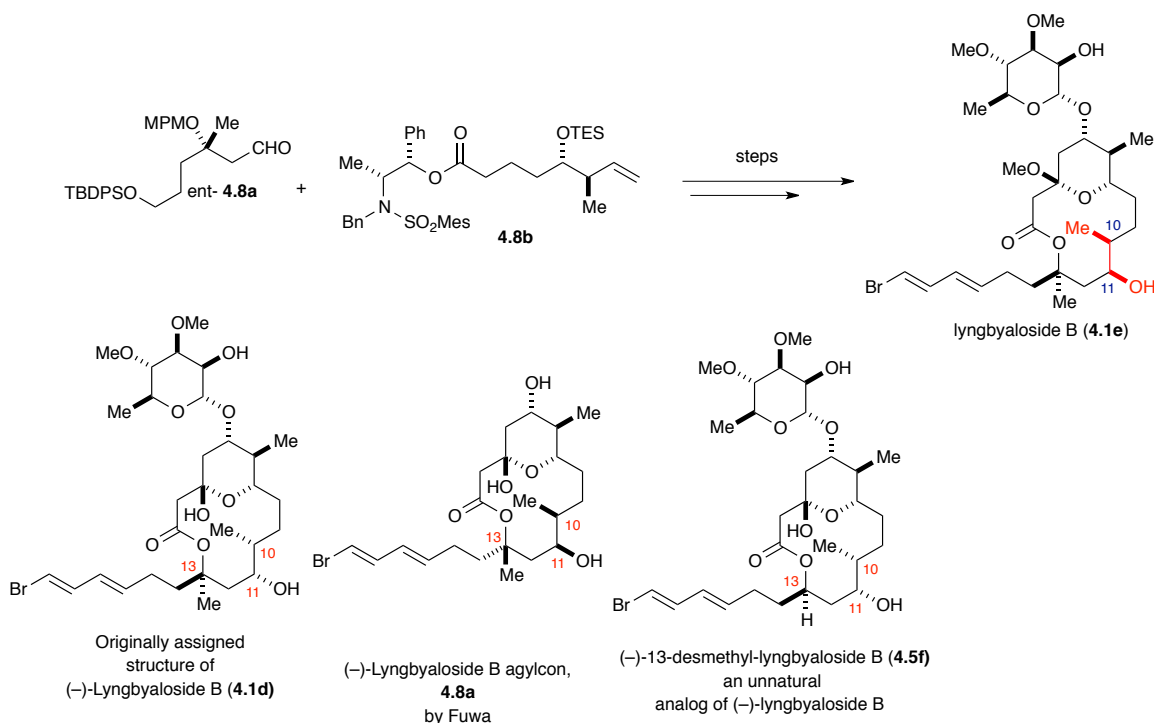


Figure 4.8. (–)-Lyngbyaloside B and its unnatural derivatives.

4.4. Results and Discussion

4.4.1. Proposed retrosynthetic analysis of (–)-13-desmethyl-lynbouilloside (4.1c)

Inspired by these efforts, as well as intriguing biological activity, our proposed retrosynthetic analysis revealed that (–)-13-desmethyl-lynbouilloside **4.1c** could be accomplished via glycosylation and Julia olefination of macrolactone **4.9a**, which in turn can be accessed from the β -ketoester **4.9b** via Boeckman acylketene cyclization (Figure 4.9).¹⁷ Oxidative cleavage of the terminal olefin in **4.9c**, followed by Roskamp two-carbon homologation,¹⁶ would enable the synthesis of β -ketoester **4.9b**. Olefin **4.9c** was planned from the corresponding bicyclic phosphate **4.9d** via a one-pot, sequential, three-reaction protocol consisting of Pd-catalyzed reductive allylic transposition/methylation/reductive tether removal of phosphate tether.

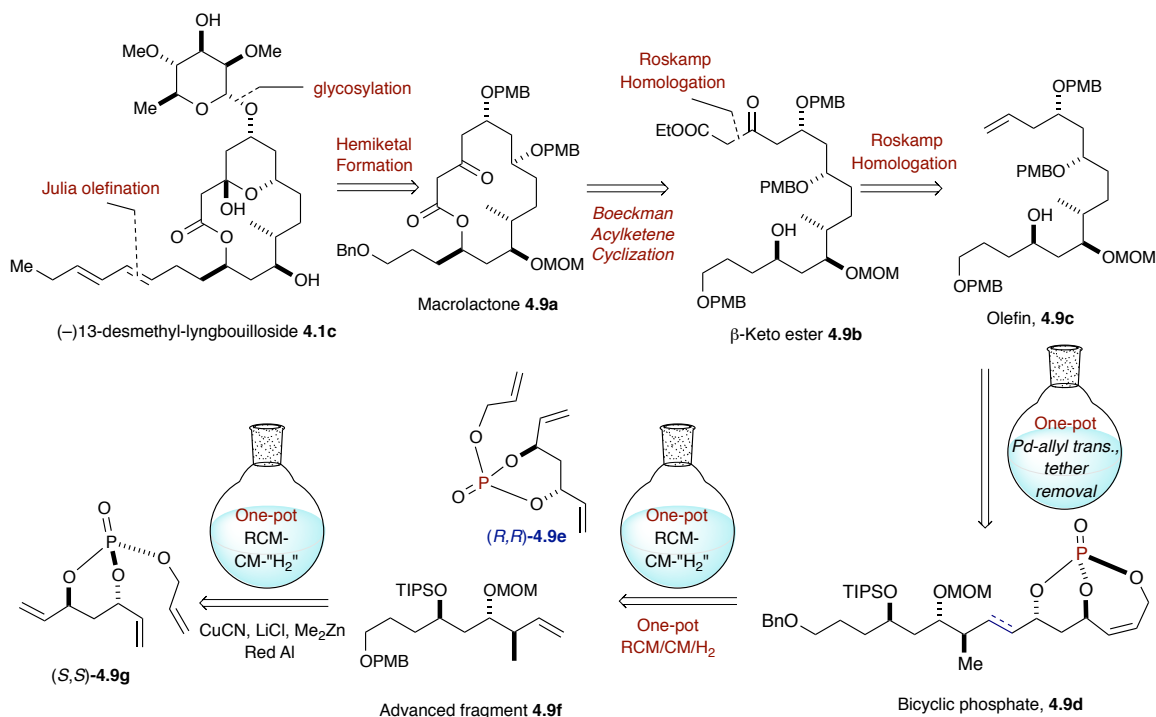


Figure 4.9. Retrosynthetic analysis of (–)-13-desmethyl-lynbouilloside.

The synthesis of the bicyclic phosphate **4.9d** was envisaged from (*R,R*)-triene **4.9e** and CM partner **4.9f** via phosphate tether-mediated one-pot sequential RCM/CM/chemoselective hydrogenation “H₂” protocol.¹⁵ The advanced fragment **4.9f** could be accomplished from (*S,S*)-triene **4.9g**, via an iterative one-pot sequential RCM/CM/“H₂” protocol, followed by a one-pot sequential TIPS/MOM protection.

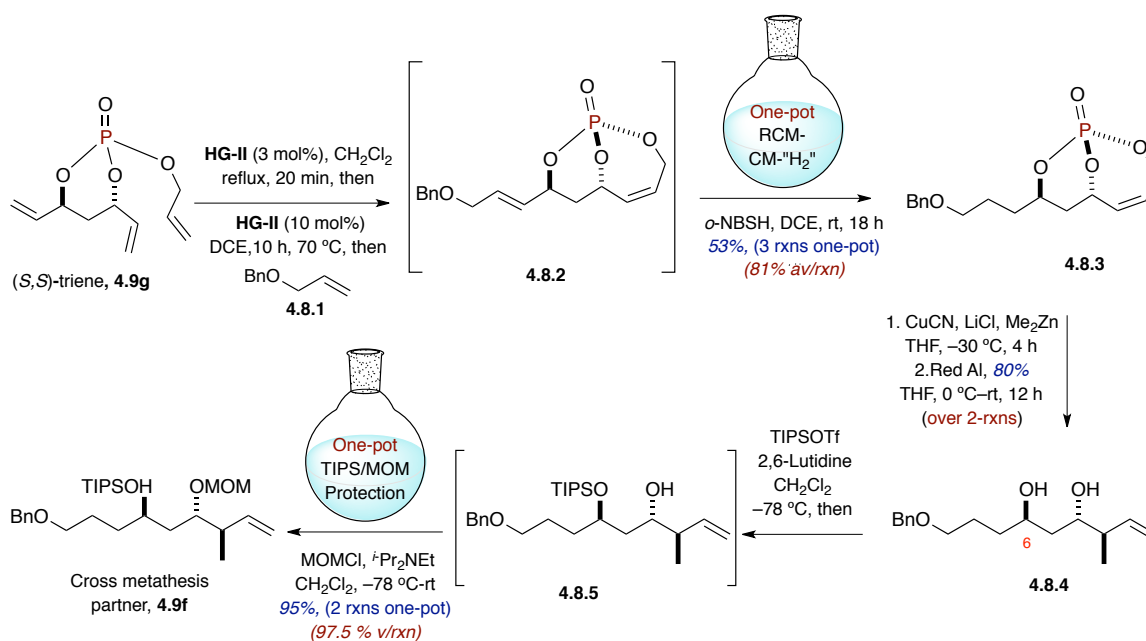
4.4.2. Forward synthesis of (–)-13-desmethyl-lynbouilloside (**4.1c**)

Toward the aforementioned goal, the forward synthesis of (–)-13-desmethyl-lynbouilloside commenced with the synthesis of CM partner **4.9f** (Scheme 4.8). Utilizing our previously developed phosphate tether-mediated one-pot sequential RCM/CM/chemoselective hydrogenation “H₂” protocol, we were able to synthesize bicyclic phosphate **4.8.3** in 53% over three reactions (81% av/rxn) in a single pot. In this regard, (*S,S*)-triene **4.9g** was first subjected to RCM reaction utilizing the **HG–II** catalyst (3 mol%). After completion of RCM, the solvent was evaporated and CM partner **4.8.1** was introduced as solution in DCE followed by the **HG–II** (6 mol%) catalyst under argon. The reaction mixture was heated to 70 °C for 6 h, and next another portion of the **HG–II** catalyst (4 mol%) and CM partner was added, and the reaction mixture stirred for an additional 4 h at 70 °C.

After complete consumption of starting material, the crude CM product **4.8.2** was subjected to chemoselective hydrogenation of the external olefin in **4.8.2** using *o*-NBSH and Et₃N (2ml/1g of *o*-NBSH) to afford the bicyclic phosphate **4.8.3** in 53% yield over three reactions in one pot (81% av/rxn). Regio- and diastereoselective allylic cuprate additions to the bicyclic phosphate **4.8.3** using CuCN, LiCl and Me₂Zn provided the acid, which was subsequently subjected to phosphate tether removal by RedAl to afford the

required triol **4.8.4** bearing a stereotriad in 80% yield over two reactions in two pots, followed by a single purification procedure. Taking advantage of the steric factor, we were able to selectively protect the alcohol at the C6 position in **4.8.4** using TIPSOTf and 2,6-lutidine. The crude product was subsequently protected as the MOM-ether using MOMCl and DIPEA in the same pot, with no solvent change to provide the CM partner **4.9f** in 95 % yield over two reactions in one-pot with 97.5% av/rxn.

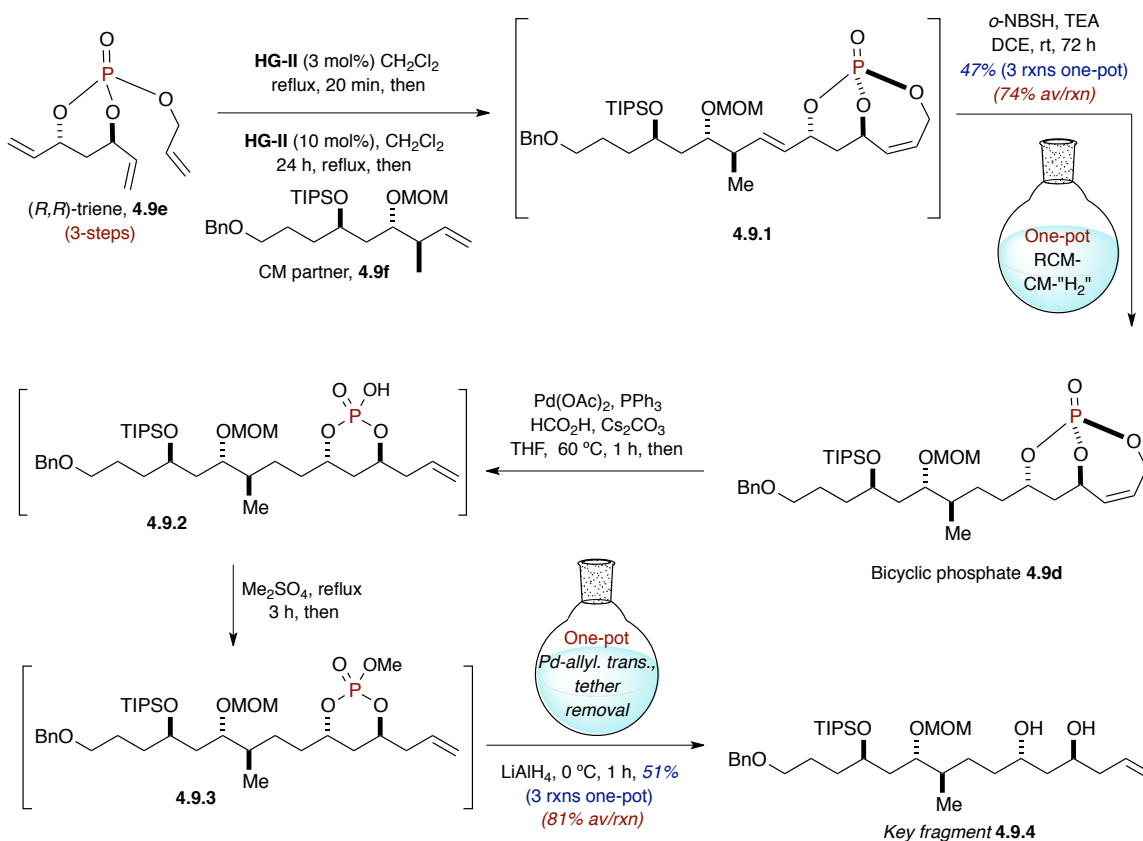
Scheme 4.8. *Synthesis of CM partner 4.9f (four pots, seven reactions).*



With the CM partner **4.9f** in hand, we carried out an iterative phosphate tether-mediated one-pot sequential RCM/CM/"H₂" protocol to assemble the bicyclic phosphate **4.9d** (Scheme 4.9). Toward this goal, (*R,R*)-triene **4.9e** was cyclized via RCM reaction using the **HG-II** catalyst (3 mol%). After completion of RCM, the solvent was evaporated and the crude bicyclic phosphate was treated with CM partner **4.9f** in DCE under argon. The reaction mixture was refluxed for 24 hours, and the **HG-II** catalyst and CM partner were added portionwise (HG-II = 0.6 mol%, 0.2 mol%, 0.2 mol%, (*R,R*)-

triene **4.9f** = 1.2 equiv., 0.2 equiv., 0.2 equiv.) after 10, 8 and 6 hours, respectively. After completion of the CM reaction, crude product **4.9.1** was subjected to chemoselective hydrogenation “H₂” reaction using *o*-NBSH and Et₃N (2mL of Et₃N/1g of *o*-NBSH) at room temperature.

Scheme 4.9. Synthesis of key fragment **4.9.4** (six reactions in two pots).

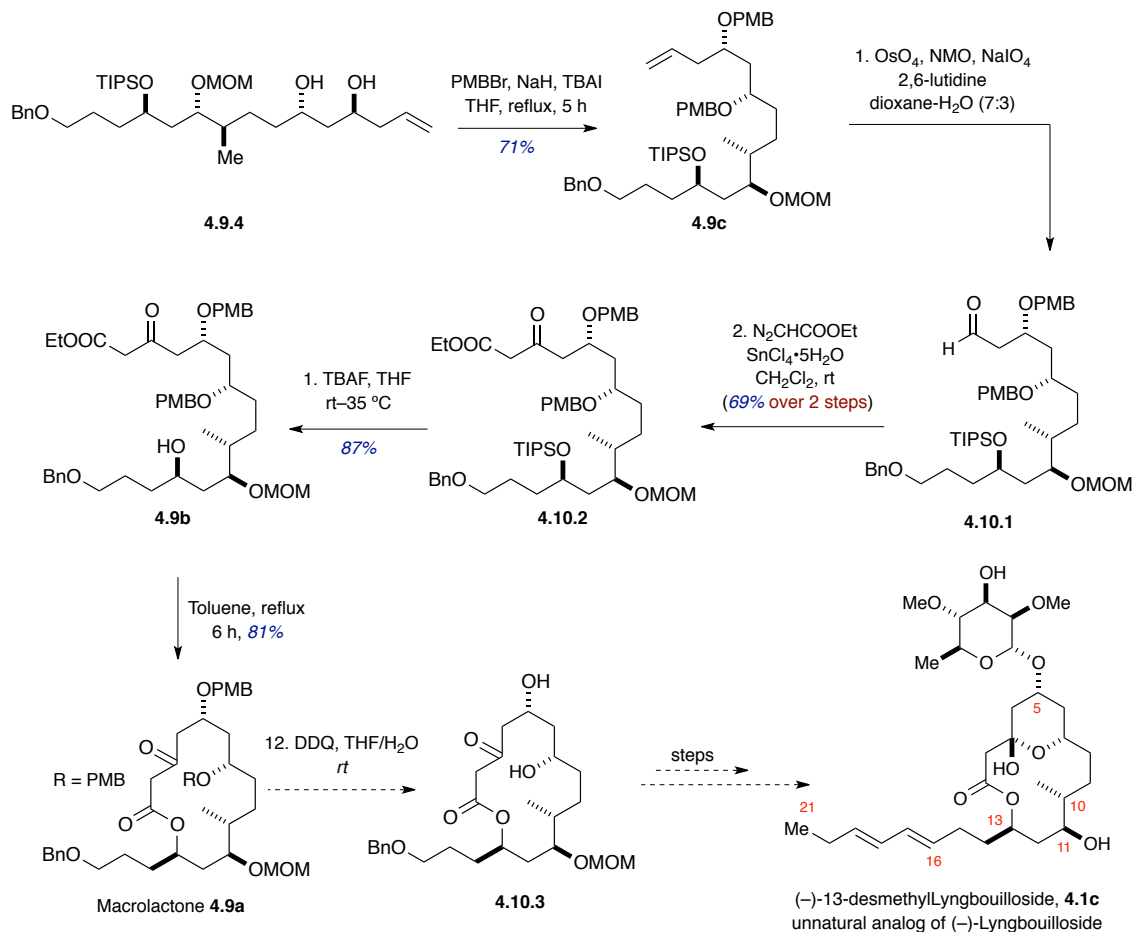


It should be noted, that for the chemoselective hydrogenation of the external olefin in the crude CM product **4.9.1**, five equivalents of *o*-NBSH and Et₃N (2mL of Et₃N/1g of *o*-NBSH) were added sequentially every 8 hours and the reaction mixture was stirred for 72 hours at room temperature. The bicyclic phosphate **4.9d** was obtained in 47% yield over three reactions in one-pot with 74% av/rxn.

The bicyclic phosphate **4.9d** was subjected to a one-pot sequential Pd-catalyzed reductive allylic transposition/methylation/reductive tether removal protocol³⁷ furnishing 1,3-*anti*-diol fragment **4.9.4** in 51% yield over a three reaction-sequence in one-pot (81% av/rxn). This one-pot processes began with Pd-catalyzed reductive allylic transposition [Pd(OAc)₂, PPh₃, HCOOH, Cs₂CO₃] to afford the terminal olefin **4.9.2**, which was subsequently methylated in the same pot with no solvent change using dimethyl sulfate (Me₂SO₄). After methylation, the phosphate tether was removed under reductive conditions, using LiAlH₄, to afford the key fragment **4.9.4** in 51% yield over three reactions in one-pot (81% av/rxn).

With 1,3-*anti* diol **4.9.4** in hand, PMB-protection of the 1,3-*anti*-diol in **4.9.4** using PMBBBr (NaH, THF) afforded the PMB-protected alcohol **4.9c** in 71% yield (Scheme 4.10). Oxidative cleavage of the terminal olefin in **4.9c** using a modified Johnson-Lemieux protocol developed by Jin and coworkers²³ (OsO₄, NaIO₄, 2,6-lutidine) provided the corresponding aldehyde **4.10.1**. Without further purification, the crude aldehyde **4.10.1** was subjected to a two-carbon Roskamp homologation¹⁶ using ethyl diazoacetate and SnCl₄•5H₂O to afford the β -keto ester **4.10.2** in 69% overall yield, over two reactions in two pots and one purification procedure. Next, we deprotected the TIPS-group using TBAF to afford the Boeckman cyclization precursor **4.9b** in 87% yield. Thermolysis of the β -keto ester **4.9b** in toluene (0.0007 M) using a Dean-Stark condenser afforded the macrolactone **4.9a** in 81% yield. So far, we are at this stage of the synthesis of (–)-13-desmethyl-lyngbouilloside (**4.1c**), further studies towards the completion of the molecule are in progress.

Scheme 4.10. Synthesis of macrolactone core of (–)-13-desmethyl-lyngbouillose.



4.5. Conclusion

In summary, we have accomplished the asymmetric synthesis of the macrolactone core **4.9a** of (–)-13-desmethyl-lyngbouillose (**4.1c**) from readily prepared (*R,R*)-**4.9e**- and (*S,S*)-**4.9g** phosphate trienes. This efficient route highlights phosphate tether mediated process, which establish asymmetry and one-pot sequential protocol, which enabled the synthesis of the macrolactone core **4.9a** in 11 longest linear pot sequence with a total of 18 reactions. This pot economical approach included four one-pot sequential operations, which minimized workup and chromatographic purification procedures, thus reducing waste generation and saving time. Efforts toward the

completion of the molecule **4.1c** are underway and will be reported in due course. Overall, this approach will enable the expedient syntheses of (–)-13-desmethyl-lyngbouillose (**4.1c**) and structurally diverse analogs of (–)-lyngbouillose (**4.1a**).

4.6. References Cited

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Chapter-5

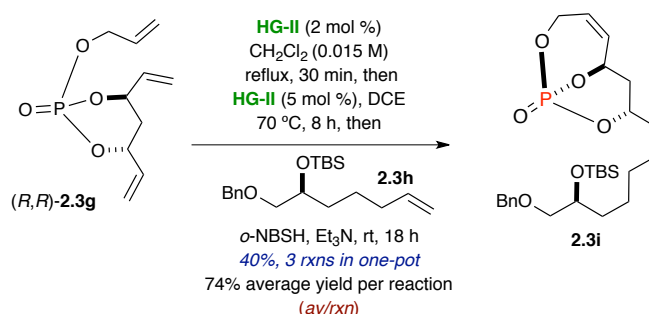
Supporting Information for Chapters 2–4: Methods, Experimental Data, and NMR Spectra

General Experimental Section

All reactions were carried out in oven- or flame-dried glassware under argon atmosphere using standard gas-tight syringes, cannulae, and septa. Stirring was achieved with oven-dried magnetic stir bars. Et₂O, THF and CH₂Cl₂ were purified by passage through a purification system (Solv-Tek) employing activated Al₂O₃ (Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. Safe and Convenient Procedure for Solvent Purification *Organometallics* **1996**, *15*, 1518–1520). Et₃N was purified by passage over basic alumina and stored over KOH. Butyllithium was purchased from Aldrich and titrated prior to use. All olefin metathesis catalysts were acquired from Materia and used without further purification. Flash column chromatography was performed with Sorbent Technologies (30930M-25, Silica Gel 60A, 40-63 μm) and thin layer chromatography was performed on silica gel 60F254 plates (EM-5717, Merck). ¹H, ¹³C, and ³¹P NMR spectra were recorded on either a Bruker DRX-400 or Bruker DRX-500 MHz spectrometers operating at 400 MHz or 500 MHz for ¹H NMR, 101 MHz or 126 MHz for ¹³C NMR, and 162 MHz for ³¹P NMR using CDCl₃ or Methanol-d₄ as solvents. The ¹H NMR data are reported as the chemical shift in parts per million, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; p, pentet; m, multiplet), coupling constant in hertz, and number of protons. High-resolution mass spectrometry (HRMS) was recorded on a LCT Premier Spectrometer (Micromass UK Limited) operating on ESI (MeOH). Observed rotations at 589 nm were measured using AUTOPOL IV Model automatic polarimeter. IR was recorded on Shimadzu FTIR-8400S instrument.

5.1: Modular Synthesis of Novel Macrocycles Bearing α,β -Unsaturated Chemotypes via a Series of One-Pot, Sequential Protocols (Chapter-2).

One-pot RCM/CM/Chemoselective “H₂”: (**1R,6R,8S**)-8-((**S**)-7-(Benzyloxy)-6-((*tert*-butyldimethylsilyl)oxy)heptyl)-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-ene 1-oxide (**2.3i**):



To a stirring solution of (*R,R*)-triene **2.3g** (100 mg, 0.43 mmol)¹ in a freshly distilled, freeze-degas-thawed CH₂Cl₂ (28 mL, 0.015 M) was added Hoveyda-Grubbs 2nd Gen. catalyst (**HG-II**) (5.4 mg, 2 mol %). The reaction mixture was refluxed (40 °C) for 30 min. After completion of RCM reaction (monitored via TLC), the solvent was evaporated and cross metathesis partner **2.3h** (215 mg, 0.65 mmol)² in a freshly distilled (FDT) 1,2-dichloroethane (DCE) (6.3 mL, 0.07 M) was added followed by the addition of **HG-II** catalyst (8 mg, 3 mol %). After being stirred for 4 h at 70 °C, a second portion of **HG-II** (5.4 mg 2 mol %) and cross-metathesis partner **2.3h** (143 mg 0.43 mmol) were added. The reaction mixture was stirred for further 4 h at 70 °C (until TLC showed the consumption of starting materials). The reaction mixture was cooled to room temperature and *o*-nitrobenzenesulfonyl hydrazine (*o*-NBSH) (900 mg, 4.3 mmol) and Et₃N (1.8 mL, at 2 mL/g) were added and stirred for 12 h (Note: the reaction flask was wrapped with

[1]. For the preparation of (*R,R*)-**4**, see: a) A. Whitehead, M. D. McReynolds, J. D. Moore, P. R. Hanson, P. R. *Org. Lett.* **2005**, 7, 3375–3378; b) A. Whitehead, M. D. McReynolds, J. D. Moore, P. R. Hanson, P. R. *Org. Lett.* **2006**, 8, 2657; c) P. K. M. Venukadasula, R. Chegondi, S. Maitra, P. R. Hanson, *Org. Lett.* **2010**, 12, 1556–1559.

[2]. Rui, W. Boland, *J. Org. Chem.* **2010**, 75, 3958–3964.

aluminum foil to avoid decomposition of *o*-NBSH due to light). After 12 h, another 5 equiv. of *o*-NBSH (450 mg, 2.15 mmol) and Et₃N (1.8 mL, at 2 mL/g) were added. The reaction mixture was stirred for another 6 h until crude NMR showed the starting material was consumed completely. The reaction mixture was diluted with EtOAc and sat. NaHCO₃ was added. The organic layer was extracted with EtOAc (3x200 mL) and the combined organic layers were washed with brine, dried (Na₂SO₄) and concentrated under reduced pressure. The crude compound was purified by flash column chromatography (hexane/EtOAc 1:3) to afford bicyclic phosphate **2.3i** [90 mg, 40% yield over 3 reactions, 74% average yield per reaction (av/rxn)] as a colorless viscous liquid. TLC (hexane/ethyl acetate 1/3): R_F: 0.48.

FTIR (neat): 2929, 2854, 2358, 1471, 1303, 1253, 1103, 1072, 972, 835, 773 cm⁻¹.

Optical Rotation: $[\alpha]_D^{23} = -79.6$ (*c* 1.0, CHCl₃).

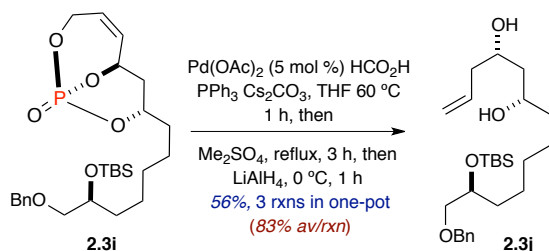
¹H NMR (500 MHz, CDCl₃): δ 7.37–7.27 (m, 5H), 6.03 (dddd, *J* = 12.0, 8.9, 5.4, 2.2 Hz, 1H), 5.59 (ddd, *J* = 11.8, 4.0, 2.5 Hz, 1H), 5.23–5.13 (m, 1H), 5.00 (ddt, *J* = 14.8, 5.7, 2.8 Hz, 1H), 4.60–4.54 (m, 1H), 4.53 (d, *J* = 1.2 Hz, 2H), 4.37 (ddd, *J*_{HP} = 27.7, *J*_{HH} = 14.7, 6.7 Hz, 1H), 3.84–3.77 (m, 1H), 3.39 (dd, *J* = 9.7, 5.6 Hz, 1H), 3.35 (dd, *J* = 22.5, 9.7, 5.5 Hz, 1H), 2.16 (ddd, *J* = 18.2, 11.8, 6.5 Hz, 1H), 1.79–1.67 (m, 2H), 1.59–1.47 (m, 2H), 1.47–1.34 (m, 2H), 1.34–1.23 (m, 5H), 0.88 (s, 9H), 0.051 (s, 3H), 0.045 (s, 3H).

¹³C NMR (126 MHz, CDCl₃): δ 138.7, 130.1, 128.5 (2), 128.1, 127.8 (2), 127.7, 77.4, 75.0, 73.5, 71.6, 63.2, 63.1, 35.9, 35.8, 35.0 (d, *J*_{CP} = 5.9 Hz), 34.8, 29.6, 26.1 [(3), SiMe₃], 25.3, 24.8, -4.1, -4.5.

³¹P NMR (162 MHz, CDCl₃): δ -3.75.

HRMS: calculated for C₂₆H₄₃NaO₆PSi (M+Na)⁺ 533.2464; found 533.2465 (TOF MS ES⁺).

(4*S*,6*S*,12*S*)-13-(Benzyloxy)-12-((*tert*-butyldimethylsilyl)oxy)tridec-1-ene-4,6-diol (2.3j):



To a stirring solution of bicyclic phosphate **2.3i** (245 mg, 0.48 mmol) in THF (1.6 mL, 0.3 M) under argon was added Cs₂CO₃ (780 mg, 2.4 mmol) and HCO₂H (48 μL, 1.2 mmol). Next, a solution of 5 mol % Pd(OAc)₂ (7.7 mg, 0.024 mmol) and PPh₃ (12 mg, 0.048 mmol) in THF (1.6 mL) under argon was immediately transferred *via* cannulae to the reaction mixture. The reaction mixture was stirred at 60 °C for 1 h (monitored by TLC). After 1 h, all starting materials were consumed and the color of reaction mixture turned black. After the reaction was complete, dimethylsulfate (Me₂SO₄) was added and the reaction mixture was refluxed for 3 h (TLC showed that phosphate acid was methylated completely). The reaction mixture was cooled to 0 °C, then LiAlH₄ (53 mg, 1.44 mmol) was added portion-wise. Next, the reaction mixture was stirred at 0 °C for 1 h. After the completion of reduction, it was quenched following the Fieser workup³ *via* slow sequential addition of H₂O (1 mL/g of LiAlH₄), followed by 10%

[3]. L. F. Fieser, M. Fieser in *Reagents for Organic Synthesis*, Vol. 1, Wiley: New York, **1967**, pp. 581–595; b) V. M. Mićović, M. Mihailović, *J. Org. Chem.* **1953**, 18, 1190–1200.

NaOH (1 mL/g of LiAlH₄) and finally H₂O (3 mL/g of LiAlH₄) and the ice bath was removed and the reaction mixture was stirred for 2 h. The reaction mixture was filtered, extracted with EtOAc (3x50 mL) and dried (Na₂SO₄). The resulting solution was filtered again, concentrated and purified using a short silica gel flash column chromatography (hexane/EtOAc 3:1), which afforded the TBS-protected diol **2.3j** (120 mg, 56% yield over 3 reactions in one-pot, 83% av/rxn) as a colorless liquid. TLC (hexane/ethyl acetate 3/1): R_f: 0.22.

FTIR (neat): 3402, 2929, 2854, 1720, 1641, 1460, 1452, 1359, 1253, 1110, 1047, 912, 835 cm⁻¹.

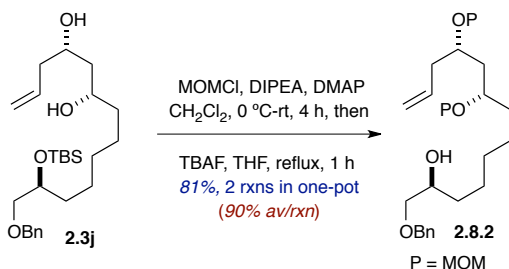
Optical Rotation: $[\alpha]_D^{23} = -1.5$ (*c* 0.8, CHCl₃).

¹H NMR (500 MHz, CDCl₃): δ 7.38–7.27 (m, 5H), 5.90–5.73 (m, 1H), 5.23–5.08 (m, 2H), 4.53 (s, 2H), 4.03–3.97 (m, 1H), 3.97–3.90 (m, 1H), 3.84–3.78 (m, 1H), 3.40 (dd, *J* = 10.0, 5.5 Hz, 1H), 3.36 (dd, *J* = 9.6, 5.4 Hz, 1H), 2.36–2.22 (m, 3H), 1.66–1.60 (m, 2H), 1.59–1.50 (m, 2H), 1.49–1.37 (m, 3H), 1.36–1.25 (m, 4H), 0.89 (s, 9H), 0.056 (s, 3H), 0.049 (s, 3H).

¹³C NMR (126 MHz, CDCl₃): δ 138.7, 134.9, 128.5 (2), 127.8 (2), 127.7, 118.5, 75.0, 73.5, 71.7, 69.5, 68.4, 42.3, 42.1, 37.7, 34.9, 30.0, 26.1 [(3), SiMe₃], 26.0, 25.4, 18.4, -4.1, -4.5.

HRMS: calculated for C₂₆H₄₆NaO₄Si (M+Na)⁺ 473.3063; found 473.3049 (TOF MS ES+).

(2*S*,8*S*,10*S*)-1-(Benzyloxy)-8,10-bis(methoxymethoxy)tridec-12-en-2-ol (2.8.2):



To a stirring solution of TBS-protected diol **2.3j** (72 mg, 0.16 mmol) in CH₂Cl₂ (1.6 mL, 0.1 M) was added *N,N*-diisopropylethylamine (DIPEA) (195 μ L, 1.12 mmol) and 4-dimethylaminopyridine (DMAP) (2 mg, 0.016 mmol). The reaction mixture was cooled to 0 °C and chloromethyl methyl ether (MOMCl) (60 μ L, 0.8 mmol) was added drop wise and the reaction mixture was stirred at room temperature for 4 h (monitored via TLC). After completion of reaction, the solvent was evaporated. To a solution of crude reaction mixture in THF (1.6 mL, 0.1 M) was added TBAF (290 μ L, 0.48 mmol) drop wise and the reaction mixture was refluxed for 1 h (reaction was monitored *via* TLC). After complete consumption of the starting material, it was quenched with aqueous ammonium chloride (NH₄Cl), extracted with EtOAc (3x20 mL), dried (Na₂SO₄), filtered and concentrated under reduced pressure. The crude compound was purified by silica gel chromatography (hexane/EtOAc 10:1) to furnish the MOM-protected alcohol **2.8.2** (51 mg, 81% yield over two steps, 90% av/rxn) as a colorless viscous liquid. TLC (hexane/ethyl acetate 4/1): R_f: 0.41.

TIR (neat): 3479, 2927, 2854, 1454, 1215, 1147, 1099, 1041, 916, 771 cm⁻¹.

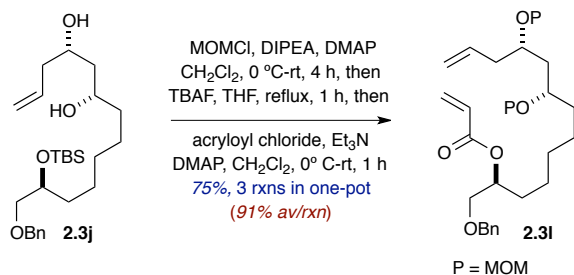
Optical Rotation: $[\alpha]_D^{23} = +3.6$ (*c* 0.25, CHCl₃).

¹H NMR (400 MHz, CDCl₃): δ 7.40–7.29 (m, 5H), 5.89–5.76 (m, 1H), 5.15–5.04 (m, 2H), 4.73–4.63 (m, 4H), 4.57 (s, 2H), 3.86–3.75 (m, 2H), 3.70 (p, J = 5.6 Hz, 1H), 3.51 (dd, J = 9.4, 3.0 Hz, 1H), 3.40 (s, 3H), 3.39 (s, 3H), 3.33 (t, J = 8.7 Hz, 1H), 2.34 (t, J = 8.5 Hz, 2H), 1.64–1.39 (m, 7H), 1.39–1.21 (m, 5H).

¹³C NMR (126 MHz, CDCl₃): δ 138.2, 134.6, 128.7 (2), 128.01, 127.95 (2), 117.7, 96.3, 96.2, 75.4, 74.9, 74.8, 73.6, 70.6, 55.9, 55.9, 40.4, 40.1, 35.4, 33.2, 30.1, 25.7, 25.1.

HRMS: calculated for C₂₄H₄₀NaO₆ (M+Na)⁺ 447.2723; found 447.2735 (TOF MS ES+).

2*S*,8*S*,10*S*)-1-(Benzyloxy)-8,10-bis(methoxymethoxy)tridec-12-en-2-yl acrylate (2.3l):



To a stirring solution of TBS-protected diol **2.3j** (15 mg, 0.033 mmol) in CH₂Cl₂ was added DIPEA (25 μ L, 0.2 mmol) and DMAP (0.42 mg, 0.003 mmol). The reaction mixture was stirred for 15 min, cooled to 0 °C and added MOMCl (10.1 μ L, 0.13 mmol) drop wise. The reaction mixture was stirred at room temperature for 4 h (monitored by TLC). After completion of reaction, the solvent was evaporated and to the crude reaction mixture was added THF (0.3 mL, 0.1 M) followed by drop wise addition of TBAF (50 μ L, 0.16 mmol) at room temperature. The reaction mixture was refluxed for 1 h (monitored *via* TLC). After completion of reaction, the solvent was evaporated and CH₂Cl₂ (0.3 mL, 0.1 M) was added, followed by Et₃N (27 μ L 0.198 mmol) and DMAP

(0.4 mg, 0.0033 mmol). The reaction mixture was cooled to 0 °C, added acryloyl chloride (5.3 µL, 0.066 mmol) drop wise and stirred at room temperature for 1 h (monitored via TLC). After completion, it was quenched with ice water, extracted with CH₂Cl₂ (3x10 mL), dried (MgSO₄) and concentrated. The compound was purified using silica gel chromatography (hexane/EtOAc 15:1), which afforded the **2.3I** (12 mg, 75% yield over 3 reactions, 91% av/rxn) as a viscous liquid. TLC (hexane/ethyl acetate 3/1): R_f: 0.51.

FTIR (neat): 2931, 1724, 1406, 1269, 1195, 1099, 1043, 916, 810 cm⁻¹.

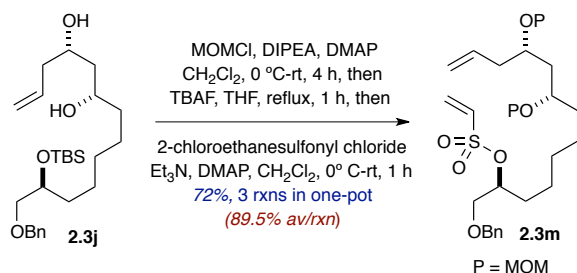
Optical Rotation: $[\alpha]_D^{23} = +6.5$ (*c* 0.55, CHCl₃).

¹H NMR (400 MHz, CDCl₃): δ 7.37–7.28 (m, 5H), 6.42 (dd, *J* = 17.4, 1.5 Hz, 1H), 6.15 (dd, *J* = 17.3, 10.4 Hz, 1H), 5.88–5.77 (m, 2H), 5.17–5.05 (m, 3H), 4.73–4.63 (m, 4H), 4.59 (d, *J* = 12.1, 1H), 4.51 (d, *J* = 12.1, 1H), 3.82–3.75 (m, 1H), 3.73–3.64 (m, 1H), 3.55 (d, *J* = 4.8 Hz, 2H), 3.39 (s, 3H), 3.38 (s, 3H), 2.34 (t, *J* = 4.9 Hz, 2H), 1.70–1.63 (m, 1H), 1.63–1.57 (m, 1H), 1.57–1.41 (m, 3H), 1.40–1.23 (m, 7H).

¹³C NMR (101 MHz, CDCl₃): δ 166.1, 138.3, 134.6, 130.9, 128.9, 128.6, 127.9 (2), 127.8 (2), 117.6, 96.4, 96.2, 75.4, 74.9, 73.3, 73.2, 71.3, 55.9, 55.9, 40.4, 40.1, 35.4, 31.1, 29.9, 25.5, 25.0.

HRMS: calculated for C₂₇H₄₂NaO₇ (M+Na)⁺ 501.2828; found 501.2835 (TOF MS ES+).

(2*S*,8*S*,10*S*)-1-(Benzyloxy)-8,10-bis(methoxymethoxy)tridec-12-en-2-yl ethenesulfonate (2.3m):



To a stirring solution of TBS-protected diol **2.3j** (36 mg, 0.08 mmol) in CH₂Cl₂ was added DIPEA (97 µL, 0.56 mmol) and DMAP (1.01 mg, 0.008 mmol). The reaction mixture was stirred for 15 min, cooled to 0 °C and added MOMCl (30 µL, 0.40 mmol) drop wise. The reaction mixture was stirred at room temperature for 4 h (monitored via TLC). After completion of reaction, the solvent was evaporated. To the reaction mixture was added THF (0.3 mL, 0.1 M), followed by drop wise addition of TBAF (69 µL, 0.24 mmol). The reaction was refluxed for 1 h (monitored via TLC). After completion of reaction, the solvent was evaporated and CH₂Cl₂ (0.3 mL, 0.1 M), followed by Et₃N (27 µL 0.198 mmol) and DMAP (0.4 mg, 0.0033 mmol) were added. The reaction mixture was cooled to 0 °C, added 2-chloroethane sulfonyl chloride (25 µL, 0.24 mmol) drop wise and stirred for 1 h (monitored via TLC). After completion, it was quenched with ice water, extracted with CH₂Cl₂ (3x10 mL), dried (MgSO₄), concentrated and purified using silica gel chromatography (hexane/EtOAc 12:1) to afford **2.3m** (30 mg, 72% yield over 3 reactions, 89.5% av/rxn) as a viscous liquid. TLC (hexane/ethyl acetate 3/1): R_f: 0.26.

FTIR (neat): 3431, 2931, 1637, 1454, 1363, 1172, 1099, 1041, 916, 790 cm⁻¹;

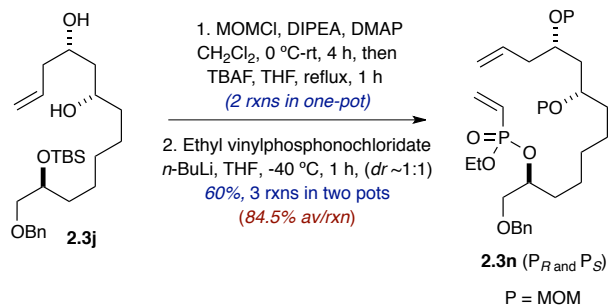
Optical Rotation: $[\alpha]_D^{23} = +12.0$ (*c* 0.5, CHCl₃);

¹H NMR (400 MHz, CDCl₃): δ 7.40–7.28 (m, 5H), 6.58 (dd, *J* = 16.6, 9.9 Hz, 1H), 6.34 (d, *J* = 16.7 Hz, 1H), 5.94 (d, *J* = 9.9 Hz, 1H), 5.88–5.76 (m, 1H), 5.14–5.05 (m, 2H), 4.74–4.63 (m, 5H), 4.57 (d, *J* = 11.8 Hz, 1H), 4.52 (d, *J* = 11.8 Hz, 1H), 3.83–3.75 (m, 1H), 3.74–3.65 (m, 1H), 3.64–3.54 (m, 2H), 3.40 (s, 3H), 3.38 (s, 3H), 2.34 (t, *J* = 6.4 Hz, 2H), 1.77–1.65 (m, 2H), 1.64–1.47 (m, 4H), 1.45–1.24 (m, 6H).

¹³C NMR (101 MHz, CDCl₃): δ 137.8, 134.6, 134.1, 128.7, 128.6, 128.1, 127.9, 117.6, 96.3, 96.3, 82.8, 75.4, 74.9, 73.6, 71.4, 55.9, 55.9, 40.4, 40.1, 35.4, 31.9, 29.8, 25.1, 24.9.

HRMS: calculated for C₂₆H₄₂NaO₈S (M+Na)⁺ 537.2498; found 537.2493 (TOF MS ES+).

(*R*/*S*_P,2*S*,8*S*,10*S*)-1-(Benzyloxy)-8,10-bis(methoxymethoxy)tridec-12-en-2-yl ethyl vinylphosphonate (2.3n, *R*_P and *S*_P):



Pot 1: To a stirred solution of TBS-protected diol **2.3j** (50 mg, 0.11 mmol) in CH₂Cl₂ (1.1 mL, 0.1 M) were added DIPEA (135 μL, 0.77 mmol) and DMAP (1.5 mg, 0.011 mmol). The reaction mixture was cooled to 0 °C, and MOMCl (41.7 μL, 0.55 mmol) was added drop wise and the reaction mixture was stirred at room temperature for 4 h (monitored via TLC). After completion of reaction, the solvent was evaporated. To the crude product in the same pot was added dry THF (1.1 mL, 0.1 M), followed by drop

wise addition of TBAF (95 μ L, 0.33 mmol) under argon. The reaction mixture was refluxed for 1 h (monitored via TLC). After completion, it was quenched with NH_4Cl and extracted with EtOAc (3x20 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude material was taken to the next pot without further purification.

Pot 2: To a solution of crude MOM-protected alcohol in THF (0.5 mL, 0.1 M) under argon was added *n*-BuLi (57 μ L, 0.14 mmol, 2.5 M in hexanes) drop wise at -40 $^{\circ}\text{C}$ and the reaction mixture was stirred for 30 min. Next, a solution of ethyl vinylphosphonochloridate (51 mg, 0.33 mmol) in THF (0.5 mL) was added slowly to the reaction mixture and stirred for 1 h at -40 $^{\circ}\text{C}$ (the reaction was monitored by TLC). After completion, the reaction mixture was quenched with aqueous NH_4Cl , extracted with EtOAc (3x10 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified *via* flash chromatography (hexane/EtOAc 1:1), which afforded an inseparable ~1:1 diastereomeric mixture of **2.3n** (36 mg, 60% yield over 3 reactions, 84.5% av/rxn) as a colorless viscous liquid. TLC (100% ethyl acetate): R_f : 0.60.

FTIR (neat): 2925, 1726, 1556, 1454, 1384, 1247, 1099, 1041, 916 cm^{-1} .

^1H NMR of two diastereomers (500 MHz, CDCl_3): δ 7.37–7.28 (m, 5H), 6.34–6.21 (m, 1H), 6.16–5.95 (m, 2H), 5.83 (ddt, $J = 17.3, 10.3, 7.1$ Hz, 1H), 5.13–5.06 (m, 2H), 4.73–4.63 (m, 4H), 4.62–4.49 (m, 3H), 4.15–4.01 (m, 2H), 3.82–3.76 (m, 0.5H of single diastereomer), 3.73–3.66 (m, 1.5H of two diastereomers), 3.63–3.51 (m, 2H), 3.41–3.37

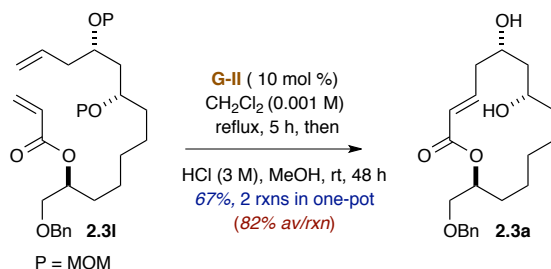
(m, 6H), 2.34 (t, $J = 5.7$ Hz, 2H); 1.73–1.57 (m, 5H), 1.56–1.44 (m, 2H), 1.42–1.24 (m, 8H).

HRMS: calculated for $C_{28}H_{47}NaO_8P$ ($M+Na$)⁺ 565.2906; found 565.2911 (TOF MS ES+).

General procedure A; One-pot, sequential RCM/MOM-deprotection.

To a degassed solution of diene (0.05 mmol) in CH_2Cl_2 (33 mL, 0.001 M) was added the **G-II** catalyst (10 mol %) and the reaction mixture was refluxed for 5–8 h (monitored *via* TLC). After completion of the reaction, the solvent was evaporated. To the crude RCM product was added 2 mL mixture of MeOH and HCl (3.0 M) in a ratio of 1:1.5, respectively. The reaction mixture was stirred at room temperature for 36–48 h (monitored *via* TLC). After completion, the reaction mixture was quenched with aqueous $NaHCO_3$ (pH ~8), extracted with CH_2Cl_2 (3x10 mL), dried (Na_2SO_4), filtered, concentrated under reduced pressure, and purified using flash chromatography to furnish the desired macrocycles.

(6*S*,8*S*,14*S*,*E*)-14-((Benzyloxy)methyl)-6,8-dihydroxyoxacyclotetradec-3-en-2-one (2.3a):



Following general procedure A, the compound **2.3a** was synthesized and purified *via* silica gel column chromatography (hexane/EtOAc 3:2), 15 mg of **2.3I** (0.031 mmol) generated 7.6 mg of **2.3a** [67% over 2 rxns in one-pot (82% av/rxn)] as a colorless viscous liquid. TLC (hexane/ethyl acetate 3/7): R_f : 0.23.

FTIR (neat): 3446, 2923, 2854, 1718, 1652, 1558, 1458, 1259, 1095, 991 cm^{-1} .

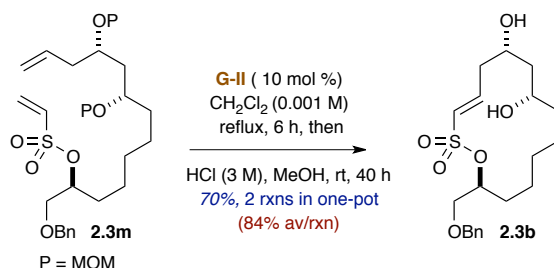
Optical Rotation: $[\alpha]_D^{23} = -2.5$ (c 0.2, CHCl_3).

^1H NMR (500 MHz, CDCl_3): δ 7.38–7.27 [m, 5H, $\text{C}_6\text{H}_5\text{CH}_2\text{O}$ –], 6.98 [ddd, $J = 15.9, 8.9, 6.2$ Hz, 1H, $-\text{CH}_2\text{CH}=\text{CHCO}$ –], 5.93 [d, $J = 15.5$ Hz, 1H, $-\text{CH}_2\text{CH}=\text{CHCO}$ –], 5.19 [p, $J = 5.9$ Hz, 1H, $-\text{CH}_2\text{OCH}_2\text{CH}(\text{O})\text{CH}_2$ –], 4.59 [d, $J = 12.1$ Hz, 1H, $\text{PhCH}_a\text{H}_b\text{OCH}_2$ –], 4.55 [d, $J = 12.1$ Hz, 1H, $\text{PhCH}_a\text{H}_b\text{OCH}_2$ –], 4.27–4.20 [m, 1H, $-\text{CH}=\text{CHCH}_2\text{CH}(\text{OH})\text{CH}_2\text{CH}(\text{OH})\text{CH}_2$ –], 4.01–3.94 [m, 1H, $-\text{CH}=\text{CHCH}_2\text{CH}(\text{OH})\text{CH}_2\text{CH}(\text{OH})\text{CH}_2$ –], 3.62 [dd, $J = 10.3, 5.9$ Hz, 1H, $\text{PhCH}_2\text{OCH}_a\text{H}_b\text{CH}(\text{O})\text{CH}_2$ –], 3.56 [dd, $J = 10.3, 4.9$ Hz, 1H, $\text{PhCH}_2\text{OCH}_a\text{H}_b\text{CH}(\text{O})\text{CH}_2$ –], 3.37–3.33 [m, 1H, $-\text{CH}_2\text{CH}(\text{OH})\text{CH}_2$ –], 2.61–2.54 [m, 1H, $-\text{CH}_a\text{H}_b\text{CH}=\text{CHCO}$ –], 2.50–2.42 [m, 1H, $-\text{CH}_a\text{H}_b\text{CH}=\text{CHCO}$ –], 1.86 [ddd, $J = 15.0, 5.8, 4.0$ Hz, 1H, $-\text{CH}_2\text{CH}(\text{OH})\text{CH}_a\text{H}_b\text{CH}(\text{OH})\text{CH}_2$ –], 1.75–1.60 [m, 3H, aliphatic], 1.55–1.45 [m, 2H, aliphatic], 1.38–1.15 [m, 6H, aliphatic].

^{13}C NMR (126 MHz, CDCl_3): δ 166.1, 146.0, 138.2, 128.6(2), 127.89(2), 127.86, 124.7, 73.4, 73.3, 71.3, 69.7, 68.5, 40.3, 39.3, 35.6, 29.5, 28.5, 24.6, 24.2.

HRMS: calculated for $\text{C}_{21}\text{H}_{30}\text{NaO}_5$ ($\text{M}+\text{Na}$) $^+$ 385.1991; found 385.2008 (TOF MS ES+).

(6*S*,8*S*,14*S*,*E*)-14-((Benzyloxy)methyl)-6,8-dihydroxy-1-oxa-2-thiacyclotetradec-3-ene 2,2-dioxide (2.3b):



Following general procedure A, the compound **2.3m** was synthesized and purified *via* silica gel column chromatography (hexane/EtOAc 1:1), 34 mg of **2.3b** (0.031 mmol) generated 18.5 mg of **2.3b** [70% over 2 rxns in one-pot (84% av/rxn)] as a semi solid. TLC (100% ethyl acetate 1/1): R_f : 0.51.

FTIR (neat): 3421, 2925, 2858, 1355, 1640, 1622, 1166, 1089, 1062, 910, 855 cm^{-1} .

Optical Rotation: $[\alpha]_D^{23} = -10.2$ (c 0.45, CHCl_3).

^1H NMR (500 MHz, CDCl_3): δ 7.39–7.28 [m, 5H, $\text{C}_6\text{H}_5\text{CH}_2\text{O}$ –], 6.92 [dt, $J = 15.2$, 7.6 Hz, 1H, $-\text{CH}_2\text{CH}=\text{CHSO}_3-$], 6.38 [dt, $J = 15.3$, 1.4 Hz, 1H, $-\text{CH}_2\text{CH}=\text{CHSO}_3-$], 4.67–4.54 [m, 3H, $\text{PhCH}_2\text{OCH}_2\text{CH}(\text{O})\text{CH}_2-$], 4.25–4.17 [m, 1H, $-\text{CH}=\text{CHCH}_2\text{CH}(\text{OH})\text{CH}_2\text{CH}(\text{OH})\text{CH}_2-$], 4.06 [dd, $J = 14.6$, 7.8 Hz, 1H, $-\text{CH}=\text{CHCH}_2\text{CH}(\text{OH})\text{CH}_2\text{CH}(\text{OH})\text{CH}_2-$], 3.72 [dd, $J = 10.7$, 4.5 Hz, 1H, $\text{PhCH}_2\text{OCH}_a\text{H}_b\text{CH}(\text{O})\text{CH}_2-$], 3.68 [dd, $J = 10.7$, 4.8 Hz, 1H, $\text{PhCH}_2\text{OCH}_a\text{H}_b\text{CH}(\text{O})\text{CH}_2-$], 3.42 [d, $J = 5.2$ Hz, 1H, $-\text{CH}_2\text{CH}(\text{OH})\text{CH}_2-$], 2.68–2.62 [m, 2H, $-\text{CH}_2\text{CH}=\text{CHSO}_3-$],

2.19 [d, $J = 3.0$ Hz, 1H, $-\text{CH}_2\text{CH}(\text{OH})\text{CH}_2-$], 1.81–1.74 [m, 3H, aliphatic], 1.68 [dd, $J = 5.4, 2.8$ Hz, 1H, aliphatic], 1.66–1.61 [m, 2H, aliphatic], 1.55–1.47 [m, 1H, aliphatic], 1.43–1.31 [m, 4H, aliphatic], 1.28–1.22 [m, 1H, aliphatic].

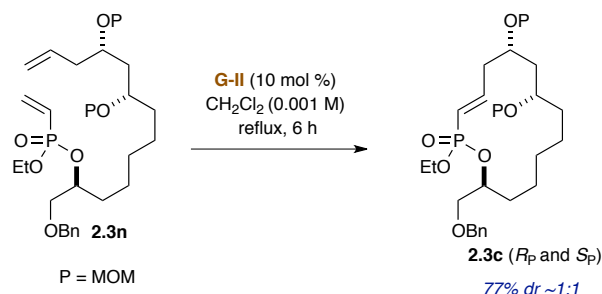
^{13}C NMR (126 MHz, CDCl_3): δ 143.6, 138.0, 128.6 (2), 127.99 (2), 127.94, 127.76, 81.7, 73.8, 71.4, 68.6, 68.5, 38.6, 38.6, 36.1, 30.3, 26.7, 24.2, 24.0.

HRMS: calculated for $\text{C}_{20}\text{H}_{30}\text{NaO}_6\text{S}$ ($\text{M}+\text{Na}$) $^+$ 421.1661; found 421.1665 (TOF MS ES $^+$).

General procedure B: Ring-closing metathesis reaction (RCM):

To a degassed solution of diene (0.05 mmol) in CH_2Cl_2 (33 mL, 0.001 M) was added **G-II** catalyst (10 mol%) and the reaction mixture was refluxed for 4-6 h (monitored *via* TLC). After completion of the reaction, solvent was evaporated. The crude compound was purified using flash chromatography, which provided the RCM product.

(*R_P* and *S_P* 6*S*,8*S*,14*S*,*E*)-14-((Benzyloxy)methyl)-6,8-bis(methoxymethoxy)-1-oxa-2-thiacyclotetradec-3-ene 2,2-dioxide (2.3c, *R_P* and *S_P*):



Following general procedure B, the diastereomers were synthesized and purified *via* silica gel flash column chromatography [diastereomer 1 (hexane/EtOAc 2:3), diastereomer 2 (hexane/EtOAc 1:2)], 20 mg of **2.3n** (0.036 mmol) generated 14.6 mg of **2.3c** (77% for two diastereomers) as a colorless viscous liquid.

Diastereomer 1 (*R_P* and *S_P*), TLC (100% ethyl acetate): R_f : 0.33:

FTIR (neat): 2925, 2854, 2378, 2341, 1456, 1245, 1147, 1097, 968, 771 cm^{-1} .

Optical Rotation: $[\alpha]_D^{23} = +27.2$ (c 0.12, CHCl_3).

^1H NMR (500 MHz, CDCl_3): δ 7.37–7.28 [m, 5H, $\text{C}_6\text{H}_5\text{CH}_2\text{O}$ –], 6.88 [dddd, $J = 22.2$, 17.1, 9.6, 5.2 Hz, 1H, $-\text{CH}_2\text{CH}=\text{CHPO}(\text{OEt})\text{O}$ –], 5.82–5.72 [m, 1H, $-\text{CH}_2\text{CH}=\text{CHPO}(\text{OEt})\text{O}$ –], 4.75–4.51 [m, 6H, $-\text{OCH}_2\text{OCH}_3$, $-\text{OCH}_2\text{OCH}_3$, $\text{PhCH}_2\text{OCH}_2$ –], 4.16–4.00 [m, 3H, $-\text{PO}(\text{OCH}_2\text{CH}_3)\text{O}$ –, $\text{PhCH}_2\text{OCH}_2\text{CH}(\text{O})\text{CH}_2$ –], 3.96–3.90 [m, 1H, $-\text{CH}=\text{CHCH}_2\text{CH}(\text{OMOM})\text{CH}_2\text{CH}(\text{OMOM})\text{CH}_2$ –], 3.76–3.69 [m, 1H, $-\text{CH}=\text{CHCH}_2\text{CH}(\text{OMOM})\text{CH}_2\text{CH}(\text{OMOM})\text{CH}_2$ –], 3.64–3.59 [m, 2H, $\text{PhCH}_2\text{OCH}_2\text{CH}(\text{O})\text{CH}_2$ –], 3.41 [s, 3H, $-\text{OCH}_2\text{OCH}_3$], 3.38 [s, 3H, $-\text{OCH}_2\text{OCH}_3$], 2.77–2.70 [m, 1H, $-\text{CH}_a\text{H}_b\text{CH}=\text{CHPO}(\text{OEt})\text{O}$ –], 2.36–2.28 [m, 1H, $-\text{CH}_a\text{H}_b\text{CH}=\text{CHPO}(\text{OEt})\text{O}$ –],

CH_aH_bCH=CHPO(OEt)O–], 1.72–1.63 [m, 3H, aliphatic], 1.62–1.55 [m, 3H, aliphatic], 1.55–1.46 [m, 1H, aliphatic], 1.45–1.19 [m, 8H, aliphatic].

³¹P NMR (162 MHz, CDCl₃): δ 17.42.

¹³C NMR (126 MHz, CDCl₃): δ 149.0 (d, J_{CP} = 5.9 Hz), 138.3, 128.5, 127.9, 122.7, 121.1, 96.1, 95.7, 75.7 (d, J_{CP} = 5.9 Hz), 73.8, 73.4, 73.0, 72.6 (d, J_{CP} = 3.0 Hz), 61.4 (d, J_{CP} = 5.9 Hz), 56.0, 55.8, 40.3, 32.4, 31.6 (d, J_{CP} = 4.8 Hz), 29.9, 27.6, 23.7, 22.8, 16.5 (d, J_{CP} = 7.1 Hz).

HRMS: calculated for C₂₆H₄₄O₈P (M+H)⁺ 515.2774; found 515.2792 (TOF MS ES+).

Diastereomer 2 (*R_P* and *S_P*), TLC (100% ethyl acetate): R_f: 0.26:

FTIR (neat): 2927, 2358, 1631, 1556, 1454, 1247, 1099, 1031, 916, 738 cm⁻¹.

Optical Rotation: $[\alpha]_D^{23} = -0.75$ (*c* 0.4, CHCl₃).

¹H NMR (500 MHz, CDCl₃): δ 7.38–7.28 [m, 5H, C₆H₅CH₂O–], 6.72 [dddd, J = 21.3, 17.1, 8.0, 6.7 Hz 1H, –CH₂CH=CHPO(OEt)O–], 5.82 [ddt, J = 21.5, 17.1, 1.3, 1H, CH₂CH=CHPO(OEt)O–], 4.71 [d, J = 6.7 Hz, 1H, –OCH_aH_bOCH₃], 4.69 [d, J = 6.7 Hz, 1H, –OCH_aH_bOCH₃], 4.65 [s, 2H, –OCH₂OCH₃], 4.57 [s, 2H, PhCH₂OCH₂–], 4.34–4.26 [m, 1H, PhCH₂OCH₂CH(O)CH₂–], 4.16–4.04 [m, 2H, –PO(OCH₂CH₃)O–], 3.97–3.90 [m, 1H, –CH=CHCH₂CH(OMOM)CH₂CH(OMOM)CH₂–], 3.83–3.76 [m, 1H, –CH=CHCH₂CH(OMOM)–CH₂CH(OMOM)CH₂–], 3.65 [dd, J = 10.3, 5.9 Hz, 1H, PhCH₂OCH_aH_bCH(O)CH₂–], 3.57 [dd, J = 10.2, 4.9 Hz, 1H, PhCH₂OCH_aH_bCH(O)CH₂–], 3.39 [s, 3H, –OCH₂OCH₃], 3.38 [s, 3H, –OCH₂OCH₃], 2.62–2.51 [m, 2H, –CH₂CH=CHPO(OEt)O–], 1.80–1.71 [m, 1H, –CH₂CH(OMOM)CH_aH_bCH–

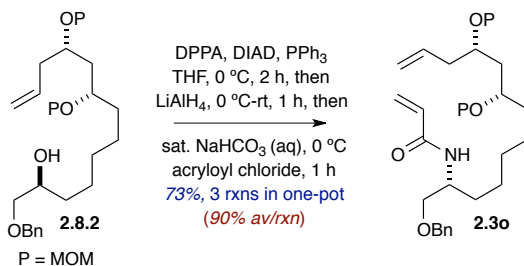
(OMOM)CH₂–], 1.71–1.61 [m, 4H, aliphatic], 1.55–1.46 [m, 1H, aliphatic], 1.46–1.21 [m, 9H, aliphatic].

³¹P NMR (162 MHz, CDCl₃): δ 14.79.

¹³C NMR (126 MHz, CDCl₃): δ 148.9 (d, *J*_{CP} = 4.0 Hz), 138.2, 128.6, 128.0, 121.5, 120.1, 96.0, 95.6, 76.8 (d, *J*_{CP} = 7.6 Hz), 73.7, 73.0, 73.1, 72.3 (d, *J*_{CP} = 3.2 Hz), 62.2 (d, *J*_{CP} = 5.9 Hz), 55.9, 55.8, 40.1, 38.7, 32.6, 31.2, 26.9, 23.6, 22.8, 16.5 (d, *J*_{CP} = 6.4 Hz).

HRMS: calculated for C₂₆H₄₃NaO₈P (M+Na)⁺ 537.2593; found 537.2597 (TOF MS ES+).

***N*-((2*R*,8*S*,10*S*)-1-(Benzyloxy)-8,10-bis(methoxymethoxy)tridec-12-en-2-yl)-acrylamide (**2.3o**):**



To a stirred solution of MOM-protected alcohol **2.8.2** (50 mg, 0.11 mmol) and PPh₃ (61.7 mg, 0.22 mmol) in dry THF (1.5 mL) was added DIAD (47.6 mg, 0.22 mmol). The reaction mixture was stirred for 5 min, DPPA (71.3 mg, 0.27 mmol) was added and the reaction mixture was stirred for 2 h at 0 °C (reaction was monitored by TLC). After completion of the reaction, LiAlH₄ (53.7 mg, 1.41 mmol) was added in portions at 0 °C and the reaction mixture was stirred for 1 h at room temperature (monitored *via* TLC, the azide was reduced to the corresponding amine). The reaction mixture was quenched with aq. saturated NaHCO₃ solution (0.75 mL), stirred for 15 min at 0 °C and diluted with THF (1.0 mL). Acryloyl chloride (32 mg, 0.33 mmol) was added at the same

temperature and the reaction mixture stirred for 1 h. After completion of the reaction, the reaction mixture was quenched with NH_4Cl , extracted with EtOAc (3x20 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The compound was purified using silica gel chromatography (hexane/EtOAc 3:1), which furnished acrylamide **2.3o** (41 mg, 73% over 3 reactions, 90% av/rxn) as colorless viscous liquid. TLC (hexane/ethyl acetate 1/1): R_f 0.32.

FTIR (neat): 3421, 2929, 2858, 1656, 1625, 1542, 1454, 1406, 1215, 1145, 1099, 916, 736 cm^{-1} .

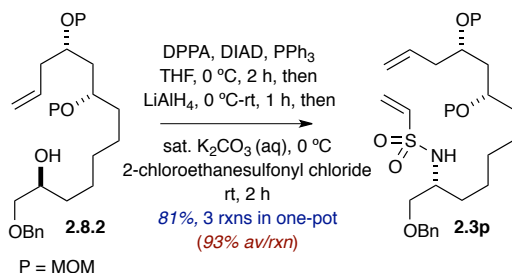
Optical Rotation: $[\alpha]_D^{23} = +40$ (c 0.65, CHCl_3).

^1H NMR (500 MHz, CDCl_3): δ 7.39–7.28 (m, 5H), 6.28 (dd, $J = 17.0, 1.5$ Hz, 1H), 6.07 (dd, $J = 16.9, 10.3$ Hz, 1H), 5.87–5.73 (m, 2H), 5.64 (dd, $J = 10.2, 1.5$ Hz, 1H), 5.14–5.05 (m, 2H), 4.73–4.63 (m, 4H), 4.54 (d, $J = 11.9$ Hz, 1H), 4.49 (d, $J = 11.9$ Hz, 1H), 4.19–4.12 (m, 1H), 3.82–3.76 (m, 1H), 3.72–3.65 (m, 1H), 3.56–3.49 (m, 2H), 3.39 (s, 3H), 3.38 (s, 3H), 2.34 (ddt, $J = 7.0, 5.7, 1.4$ Hz, 2H), 1.67–1.44 (m, 7H), 1.38–1.24 (m, 5H).

^{13}C NMR (126 MHz, CDCl_3): δ 165.1, 138.2, 134.6, 131.2, 128.7, 128.02 (2), 127.90 (2), 126.6, 117.7, 96.3, 96.2, 75.4, 74.8, 73.5, 71.6, 55.9, 55.9, 49.2, 40.3, 40.1, 35.4, 32.1, 29.9, 26.3, 25.0.

HRMS: calculated for $\text{C}_{27}\text{H}_{43}\text{NNaO}_6$ ($\text{M}+\text{Na}$) $^+$ 500.2988; found 500.2986 (TOF MS ES+).

***N*-((2*R*,8*S*,10*S*)-1-(Benzyloxy)-8,10-bis(methoxymethoxy)tridec-12-en-2-yl)ethanesulfonamide (**2.3p**):**



To a stirring solution of MOM-protected alcohol **2.8.2** (25 mg, 0.055 mmol) and PPh₃ (30.7 mg, 0.11 mmol) in dry THF (1 mL) was added DIAD (23.8 mg, 0.11 mmol) at 0 °C. The reaction mixture was stirred for 5 min, DPPA (35.6 mg, 0.13 mmol) was added and stirred for 2 h at 0 °C (monitored by TLC). After completion of the reaction, LiAlH₄ (26.8 mg, 0.70 mmol) was added in portions at 0 °C and the reaction mixture was stirred for 1 h at room temperature (monitored via TLC, the azide was reduced to the corresponding amine). The reaction mixture was quenched with aq. saturated K₂CO₃ solution (0.75 mL), stirred for 15 min at 0 °C and diluted with THF (1.0 mL). 2-Chloroethanesulfonyl chloride (17 mg, 0.16 mmol) was added at the same temperature and the reaction mixture was stirred for 2 h. After completion of the reaction, it was quenched with NH₄Cl, extracted with EtOAc (3x15 mL), dried (Na₂SO₄), and concentrated under reduced pressure. The crude compound was subjected to silica gel chromatography (hexane/EtOAc 3:1) to afford acrylamide **2.3p** (25 mg, 81% over 3 reactions, 93% av/rxn) as a colorless gummy liquid. TLC (hexane/ethyl acetate 3/7): R_f: 0.37.

FTIR (neat): 2931, 2858, 1456, 1330, 1211, 1149, 1099, 1039, 916, 734 cm⁻¹.

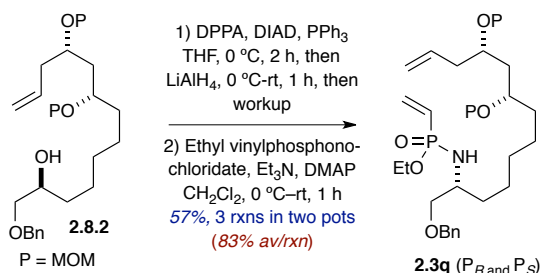
Optical Rotation: $[\alpha]_D^{23} = +7.6$ (*c* 0.5, CHCl₃).

¹H NMR (500 MHz, CDCl₃): δ 7.40–7.29 (m, 5H), 6.45 (dd, *J* = 16.6, 9.9 Hz, 1H), 6.20 (d, *J* = 16.6 Hz, 1H), 5.88–5.77 (m, 2H), 5.13–5.05 (m, 2H), 4.74–4.64 (m, 4H), 4.53–4.48 (m, 3H), 3.82–3.76 (m, 1H), 3.72–3.66 (m, 1H), 3.51 (dd, *J* = 9.4, 4.0 Hz, 1H), 3.43 (dd, *J* = 9.4, 4.1 Hz, 1H), 3.40 (s, 3H), 3.39 (s, 3H), 2.34 (ddt, *J* = 7.1, 5.8, 1.3 Hz, 2H), 1.66–1.45 (m, 7H), 1.41–1.24 (m, 5H).

¹³C NMR (126 MHz, CDCl₃): δ 137.9, 137.3, 134.5, 128.72 (2), 128.2, 128.02 (2), 125.7, 117.7, 96.3, 96.2, 75.4, 74.8, 73.5, 71.8, 55.9, 55.9, 54.1, 40.3, 40.1, 35.4, 32.9, 29.8, 26.0, 25.0.

HRMS: calculated for C₂₆H₄₃NNaO₇S (M+Na)⁺ 536.2658; found 536.2665 (TOF MS ES⁺).

Ethyl*N*-((*R/S*_P,2*R*,8*S*,10*S*)-1-(benzyloxy)-8,10-bis(methoxymethoxy)tridec-12-en-2-yl)-*P*-vinylphosphonamidate (2.3q, *R*_P and *S*_P):



The solution of MOM-protected alcohol **2.8.2** (50 mg, 0.11 mmol) and PPh₃ (61.7 mg, 0.22 mmol) in dry THF (1.5 mL) was treated with DIAD (47.6 mg, 0.22 mmol) at 0 °C and stirred for 5 min. DPPA (71.3 mg, 0.27 mmol) was added at the same temperature and stirred for 2 h. After completion of the reaction, LiAlH₄ (53.7 mg, 1.41 mmol) was added in portions at 0 °C and stirred for 1 h at room temperature (reaction was monitored via TLC, the azide was reduced to the corresponding amine). The reaction mixture was

quenched with aq. saturated NaHCO_3 solution (2.0 mL) and stirred for 15 min at 0 °C and extracted with EtOAc (3x20 mL). The combined organic layers were washed with a solution of 2.0 N HCl (2x10 mL). The combined aqueous layers were basified with saturated aq. K_2CO_3 solution (pH ~12). Then, the crude amine was extracted with EtOAc (3x20 mL) and the combined organic layers were washed with brine (15 mL), dried (Na_2SO_4) and concentrated.

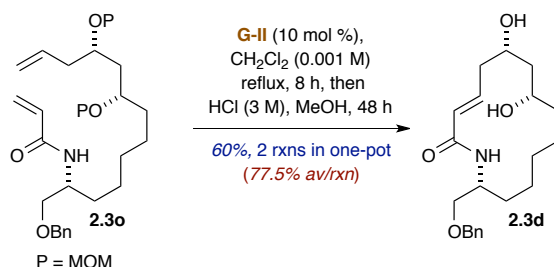
The crude amine was utilized for the next reaction without further purification. To a solution of crude amine in CH_2Cl_2 (1.0 mL) were added Et_3N (66.0 μL , 0.47 mmol) and DMAP (1.3 mg, 0.011 mmol), stirred for 5 min. A solution of ethyl vinylphosphonochloridate (50.0 mg, 0.33 mmol) in CH_2Cl_2 (0.8 mL) was added drop wise at 0 °C and stirred for 1 h at room temperature. When the TLC showed that all the amine was consumed, it was quenched with aq. NaHCO_3 solution and extracted with CH_2Cl_2 (3x10 mL), dried (Na_2SO_4) concentrated under reduced pressure and purified using silica gel flash chromatography (hexane/EtOAc 2:3) to afford two inseparable (~1:1) diastereomers of **2.3q** (36 mg, 57% yield over 3 reactions, 83% av/rxn) as a colorless viscous liquid. TLC (100% ethyl acetate): R_f : 0.38.

FTIR (neat): 2929, 2856, 1456, 1211, 1147, 1097, 1039, 958, 916, 784, 736 cm^{-1} .

^1H NMR of two diastereomers (400 MHz, CDCl_3): δ 7.39–7.29 (m, 5H), 6.25–5.99 (m, 3H), 5.95–5.76 (m, 1H), 5.15–5.05 (m, 2H), 4.74–4.62 (m, 4H), 4.51 (s, 2H), 4.09–3.95 (m, 2H), 3.79 (p, J = 5.5 Hz, 0.7H of single diastereomer), 3.74–3.64 (m, 1.3H of two diastereomers), 3.44 (dt, J = 12.2, 4.1 Hz, 2H), 3.40 (s, 3H), 3.39 (s, 3H), 3.33–3.19 (m, 1H), 2.70 (td, J = 9.9, 5.7 Hz, 1H), 2.34 (t, J = 6.4 Hz, 1H), 1.68–1.43 (m, 7H), 1.41–1.20 (m, 8H).

HRMS: calculated for $C_{28}H_{48}NNaO_7P$ ($M+Na$)⁺ 564.3066; found 564.2957 (TOF MS ES+).

(6*S*,8*S*,14*R*,*E*)-14-((Benzyloxy)methyl)-6,8-dihydroxyazacyclotetradec-3-en-2-one (2.3d):



Following general procedure A, the compound was synthesized and purified *via* silica gel flash chromatography (hexane/EtOAc 1:4), 25 mg of **2.3o** (0.055 mmol) generated 12 mg of **2.3d** [60% over 2 rxns (77.5% av/rxn)], as a colorless viscous oil. TLC (ethyl acetate /methanol 20/1): R_f : 0.22.

FTIR (neat): 3373, 3286, 2923, 2854, 1681, 1627, 1541, 1099, 1004, 813 cm^{-1} .

Optical Rotation: $[\alpha]_D^{23} = +7.7$ (c 0.35, CHCl_3).

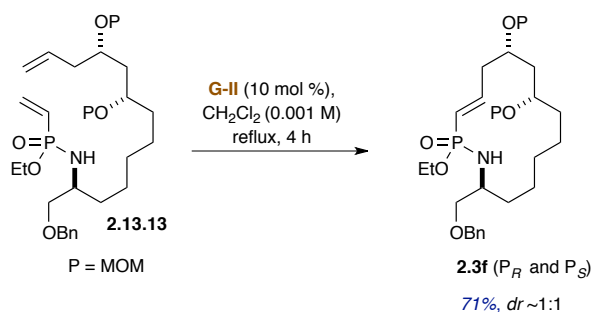
$^1\text{H NMR}$ (500 MHz, CDCl_3): δ 7.39–7.28 [m, 5H, $\text{C}_6\text{H}_5\text{CH}_2\text{O}$ –], 6.18 [ddd, J = 16.5, 8.8, 7.4 Hz, 1H, $-\text{CH}_2\text{CH}=\text{CHCONH}$ –], 5.93 [d, J = 15.1 Hz, 1H, $-\text{CH}_2\text{CH}=\text{CHCONH}$ –], 5.83 [d, J = 9.2 Hz, 1H, $-\text{CH}_2\text{CH}=\text{CHCONH}$ –], 4.55 [d, J = 11.9 Hz, 1H, $\text{PhCH}_a\text{H}_b\text{OCH}_2$ –], 4.51 [d, J = 11.9 Hz, 1H, $\text{PhCH}_a\text{H}_b\text{OCH}_2$ –], 4.20–4.09 [m, 2H, $\text{PhCH}_2\text{OCH}_2\text{CH}(\text{NH})\text{CH}_2$ –, $-\text{CH}=\text{CHCH}_2\text{CH}(\text{OH})\text{CH}_2\text{CH}(\text{OH})\text{CH}_2$ –], 4.05–3.97 [m, 1H, $-\text{CH}=\text{CHCH}_2\text{CH}(\text{OH})\text{CH}_2\text{CH}(\text{OH})\text{CH}_2$ –], 3.56 [dd, J = 9.5, 4.2 Hz, 1H, $\text{PhCH}_2\text{OCH}_a\text{H}_b\text{CH}(\text{NH})\text{CH}_2$ –], 3.51 [dd, J = 9.5, 4.2 Hz, 1H, $\text{PhCH}_2\text{OCH}_a\text{H}_b\text{CH}(\text{NH})\text{CH}_2$ –], 3.11–3.03 [m, 1H, $-\text{CH}_a\text{H}_b\text{CH}=\text{CHCONH}$ –], 2.74–2.67

CH₂CH=CHSO₂NH–], 4.64–4.55 [m, 2H, PhCH_aH_bOCH₂–, PhCH₂OCH₂CH(NH)CH₂–], 4.50 [d, J = 11.7, 1H, PhCH_aH_bOCH₂–], 4.19–4.11 [m, 1H, –CH=CHCH₂CH(OH)CH₂CH(OH)CH₂–], 4.11–4.03 [m, 1H, –CH=CHCH₂CH(OH)CH₂CH(OH)CH₂–], 3.62 [dd, J = 9.3, 4.5 Hz, 1H, PhCH₂OCH_aH_bCH(NH)CH₂–], 3.53 [dd, J = 9.3, 3.3 Hz, 1H, PhCH₂OCH_aH_bCH(NH)CH₂–], 3.44 [bs, 1H, –CH₂CH(OH)CH₂–], 3.25–3.17 [m, 1H, –CH₂CH(OH)CH₂–], 2.72–2.65 [m, 1H, –CH_aH_bCH=CHSO₂NH–], 2.55 [dt, J = 13.9, 10.7 Hz, 1H, –CH_aH_bCH=CHSO₂NH–], 2.31 [bs, 1H, –CH₂CH=CHSO₂NH–], 1.79–1.66 [m, 3H, aliphatic], 1.65–1.58 [m, 3H, aliphatic], 1.58–1.49 [m, 1H, aliphatic], 1.46–1.36 [m, 1H, aliphatic], 1.35–1.18 [m, 4H, aliphatic].

¹³C NMR (126 MHz, CDCl₃): δ 141.6, 138.1, 131.2, 128.67(2), 128.0, 127.93(2), 73.7, 72.5, 69.3, 68.7, 52.5, 38.9, 37.9, 36.3, 29.9, 26.3, 24.7, 24.5.

HRMS: calculated for C₂₀H₃₂NO₅S (M+H)⁺ 398.2001; found 398.2004 (TOF MS ES+).

(*R_P* and *S_P* 6*S*,8*S*,14*S*,*E*)-14-((Benzyloxy)methyl)-2-ethoxy-6,8-bis(methoxymethoxy)-1-aza-2-phosphacyclotetradec-3-ene 2-oxide (2.3f, *R_P* and *S_P*):



Following general procedure B, the diastereomers were synthesized and purified *via* silica gel flash column chromatography [diastereomer 1 (hexane/EtOAc 1:2), diastereomer 2 (hexane/EtOAc 1:3)], 20 mg of **2.3q** (0.036 mmol) generated 13.4 mg of **2.3f** (71% for two diastereomers) as a colorless viscous liquid.

Diastereomer 1 (*R_P* and *S_P*), TLC (100% ethyl acetate): R_f : 0.45:

FTIR (neat): 2929, 1643, 1556, 1454, 1211, 1147, 1099, 1035, 827 cm^{-1} .

Optical Rotation: $[\alpha]_D^{23} = +4.0$ (c 0.22, CHCl_3).

^1H NMR (500 MHz, CDCl_3): δ 7.37–7.28 [m, 5H, $\text{C}_6\text{H}_5\text{CH}_2\text{O}-$], 6.65 [dddd, $J = 22.4$, 16.9, 9.0, 5.6 Hz, 1H, $-\text{CH}_2\text{CH}=\text{CHPO}(\text{OEt})\text{NH}-$], 5.77 [dd, $J = 20.6$, 17.0 Hz, 1H, $-\text{CH}_2\text{CH}=\text{CHPO}(\text{OEt})\text{NH}-$], 4.70 [d, $J = 6.95$, 1H, $-\text{OCH}_a\text{H}_b\text{OCH}_3$], 4.68 [d, $J = 6.95$, 1H, $-\text{OCH}_a\text{H}_b\text{OCH}_3$], 4.65 [d, $J = 6.95$, 1H, $-\text{OCH}_a\text{H}_b\text{OCH}_3$], 4.63 [d, $J = 6.95$, 1H, $-\text{OCH}_a\text{H}_b\text{OCH}_3$], 4.56 [d, $J = 12.0$ Hz, 1H, $\text{PhCH}_a\text{H}_b\text{OCH}_2-$], 4.51 [d, $J = 12.0$ Hz, 1H, $\text{PhCH}_a\text{H}_b\text{OCH}_2-$], 4.03–3.94 [m, 2H, $-\text{PO}(\text{OCH}_2\text{CH}_3)\text{NH}-$], 3.88 [tt, $J = 7.7$, 3.5 Hz, 1H, $-\text{CH}=\text{CHCH}_2\text{CH}(\text{OMOM})\text{CH}_2\text{CH}(\text{OMOM})\text{CH}_2-$], 3.80–3.74 [m, 1H, $-\text{CH}=\text{CHCH}_2\text{CH}(\text{OMOM})\text{CH}_2\text{CH}(\text{OMOM})\text{CH}_2-$], 3.58–3.51 [m, 2H, $-\text{CH}=\text{CHCH}_2\text{CH}(\text{OMOM})\text{CH}_2\text{CH}(\text{OMOM})\text{CH}_2-$],

PhCH₂OCH₂CH(NH)CH₂–], 3.42–3.30 [m, 7H, –OCH₂OCH₃, –OCH₂OCH₃, PhCH₂OCH₂CH(NH)CH₂–], 2.75 [t, *J* = 9.5 Hz, 1H, –CH₂CH=CHPO(OEt)NH–], 2.68–2.61 [m, 1H, –CH₄H₆CH=CHPO(OEt)NH–], 2.47–2.39 [m, 1H, –CH₄H₆CH=CHPO(OEt)NH–], 1.78–1.52 [m, 5H, aliphatic], 1.51–1.38 [m, 2H, aliphatic], 1.38–1.30 [m, 3H, aliphatic], 1.30–1.19 [m, 5H, aliphatic].

³¹P NMR (162 MHz, CDCl₃): δ 20.19.

¹³C NMR (126 MHz, CDCl₃): δ 147.1 (d, *J*_{CP} = 4.5 Hz), 138.5, 128.57(2), 127.84(2), 125.2, 123.8, 96.0, 95.6, 73.9 (d, *J*_{CP} = 3.2 Hz), 73.4, 73.4, 73.1, 60.3, 60.2, 55.8, 50.4, 40.4, 38.7, 32.8 (d, *J*_{CP} = 5.1 Hz), 32.6, 27.3, 25.1, 23.5, 16.7 (d, *J*_{CP} = 6.8 Hz).

HRMS: calculated for C₂₆H₄₄NNaO₇P (M+Na)⁺ 536.2753; found 536.2767 (TOF MS ES+).

Diastereomer 2 (*R_p* and *S_p*), TLC (100% ethyl acetate): R_f: 0.35:

FTIR (neat): 2925, 2854, 1558, 1456, 1209, 1147, 1099, 1037, 950, 916 cm^{–1}.

Optical Rotation: [α]_D²³ = +18.0 (*c* 0.2, CHCl₃).

¹H NMR (400 MHz, CDCl₃): δ 7.39–7.28 [m, 5H, C₆H₅CH₂O–], 6.82–6.66 [m, 1H, –CH₂CH=CHPO(OEt)NH–], 5.83 [dd, *J* = 21.4, 17.2 Hz, 1H, , –CH₂CH=CHPO(OEt)NH–], 4.74–4.59 [m, 4H, –OCH₂OCH₃, –OCH₂OCH₃], 4.53 [s, 2H, PhCH₂OCH₂–], 4.07–3.82 [m, 3H, –PO(OCH₂CH₃)NH–, –CH=CHCH₂CH–(OMOM)CH₂CH–(OMOM)CH₂–], 3.76–3.67 [m, 1H, CH=CHCH₂CH(OMOM)CH₂CH(OMOM)CH₂–], 3.48 [dd, *J* = 9.2, 3.5 Hz, 1H, PhCH₂OCH₂CH(NH)CH₂–], 3.42–3.34 [m, 8H, –OCH₂OCH₃, –OCH₂OCH₃, PhCH₂OCH₂CH(NH)CH₂–], 2.87 [dd, *J* = 10.6, 6.5 Hz, 1H, –

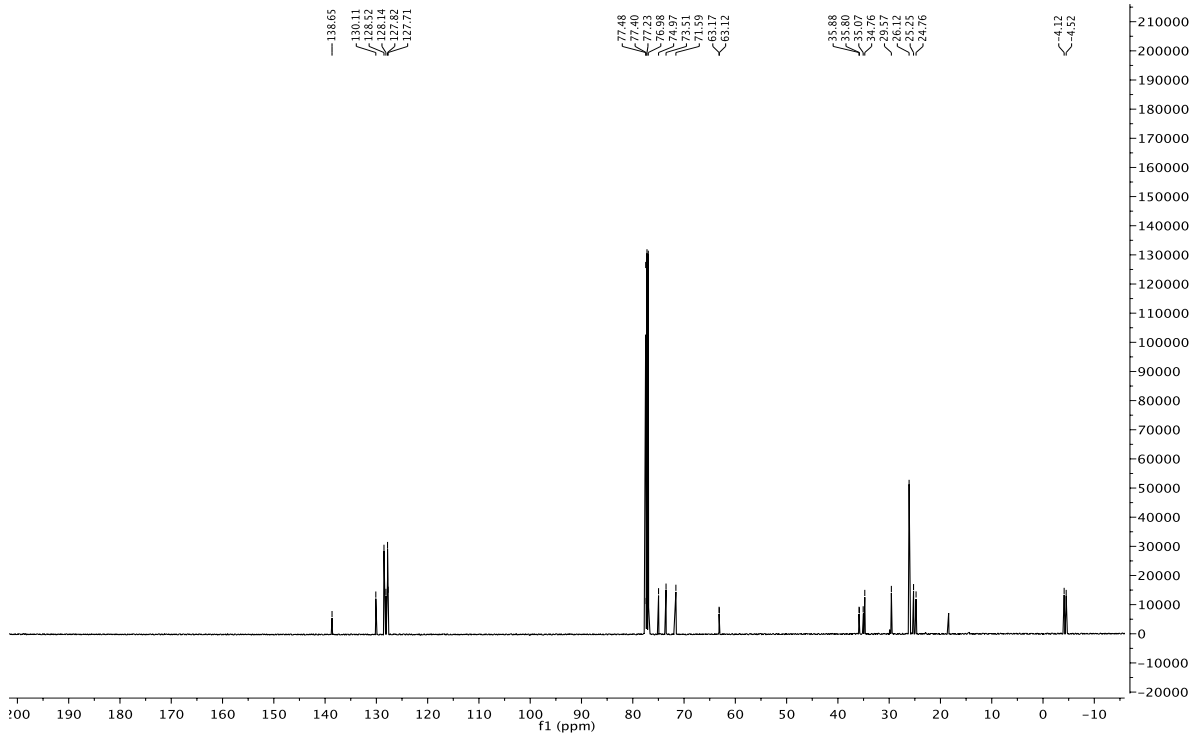
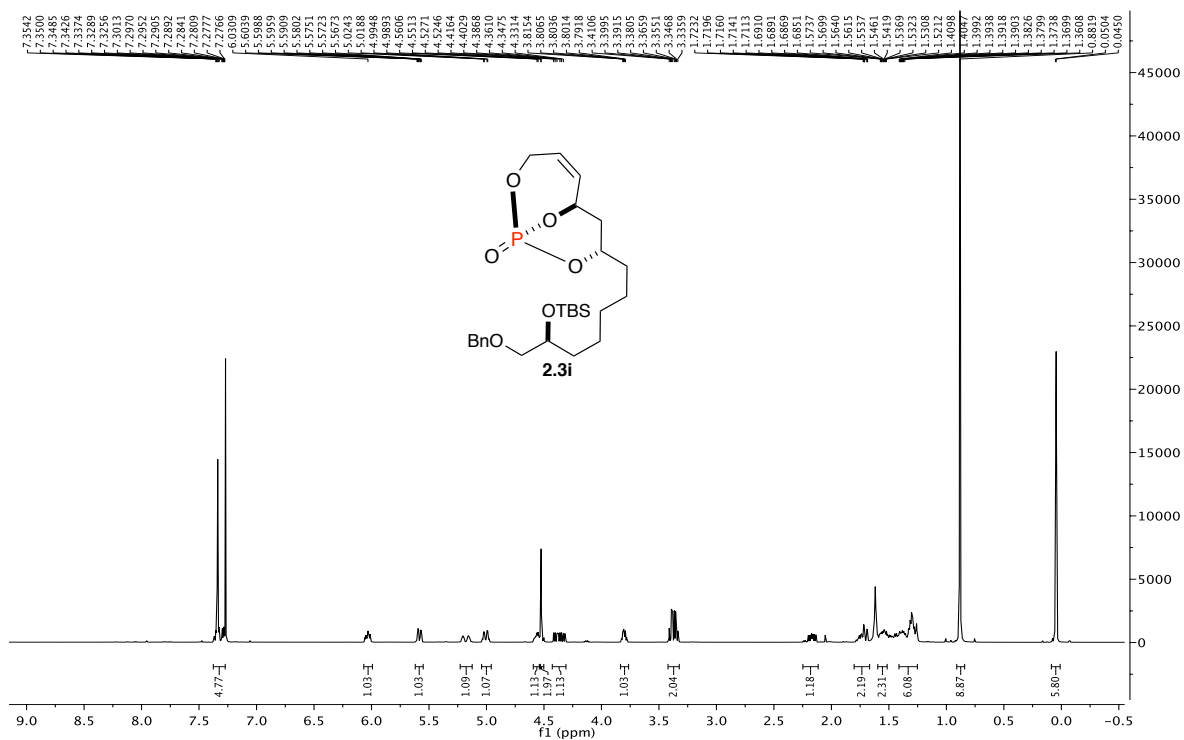
$\text{CH}_a\text{H}_b\text{CH}=\text{CHPO}(\text{OEt})\text{NH}-$], 2.72–2.62 [m, 1H, $-\text{CH}_2\text{CH}=\text{CHPO}(\text{OEt})\text{NH}-$], 2.41–2.32 [m, 1H, $-\text{CH}_a\text{H}_b\text{CHCHPO}(\text{OEt})\text{NH}-$]; 1.72–1.52 [m, 5H, aliphatic], 1.52–1.39 [m, 2H, aliphatic], 1.39–1.17 [m, 8H, aliphatic].

^{31}P NMR (162 MHz, CDCl_3): δ 20.22.

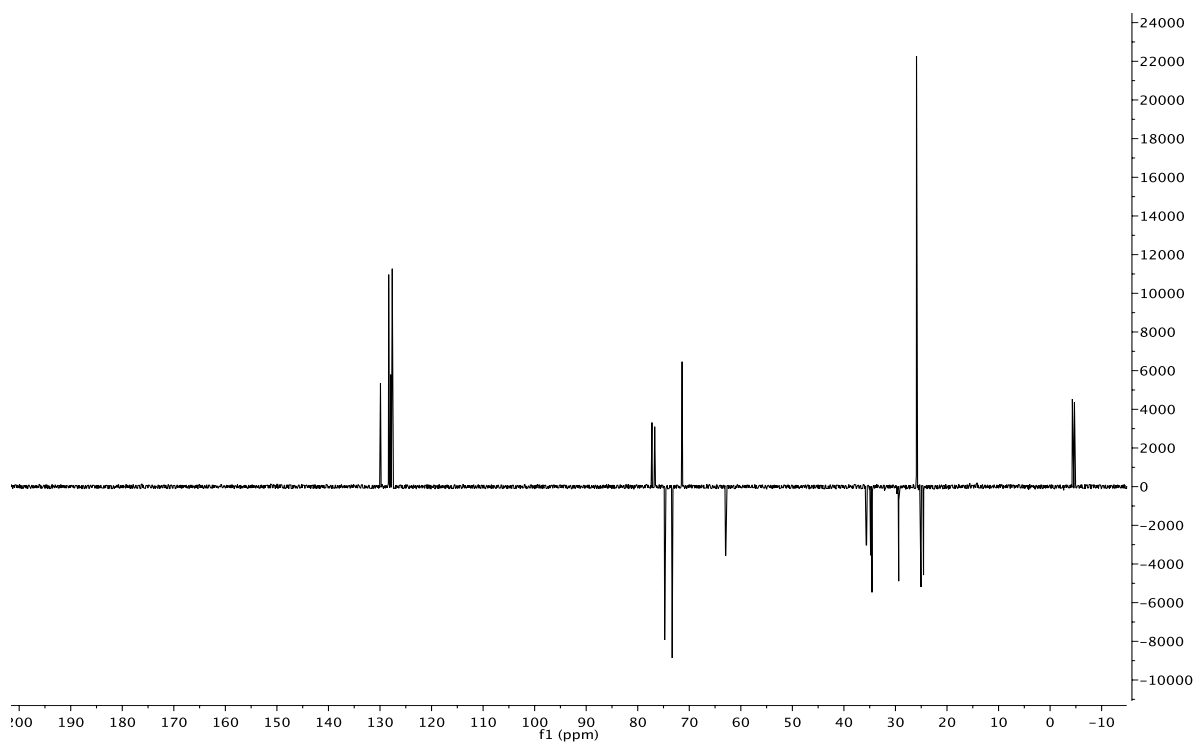
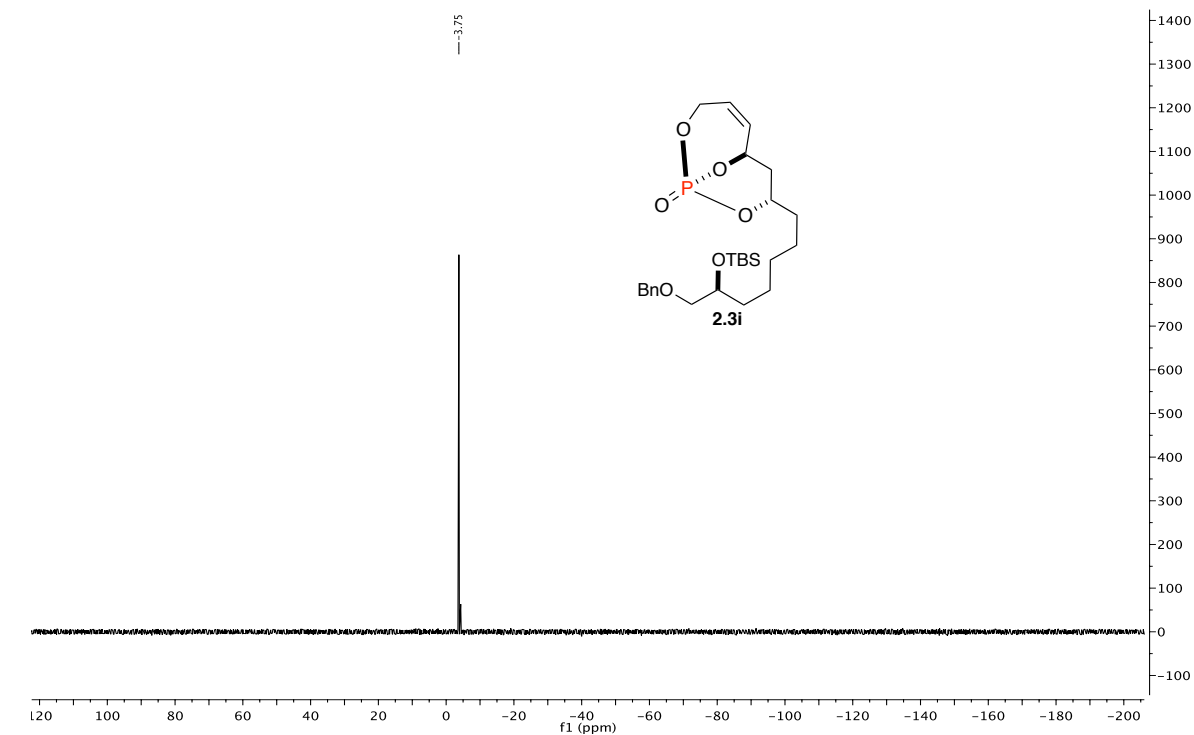
^{13}C NMR (126 MHz, CDCl_3): δ 147.3 (d, $J_{\text{CP}} = 4.1$ Hz), 138.3, 128.62(2), 127.92(2), 123.7, 122.3, 96.2, 95.8, 74.3, 73.6, 72.9, 72.8 (d, $J_{\text{CP}} = 2.5$ Hz), 59.9, 56.0 (d, $J_{\text{CP}} = 5.5$ Hz), 55.8, 50.6, 40.1, 39.4, 32.8 (d, $J_{\text{CP}} = 6.0$ Hz), 32.4, 27.7, 24.7, 22.9, 16.6 (d, $J_{\text{CP}} = 7.1$ Hz).

HRMS: calculated for $\text{C}_{26}\text{H}_{44}\text{NNaO}_7\text{P}$ ($\text{M}+\text{Na}$) $^+$ 536.2753; found 536.2755 (TOF MS ES+).

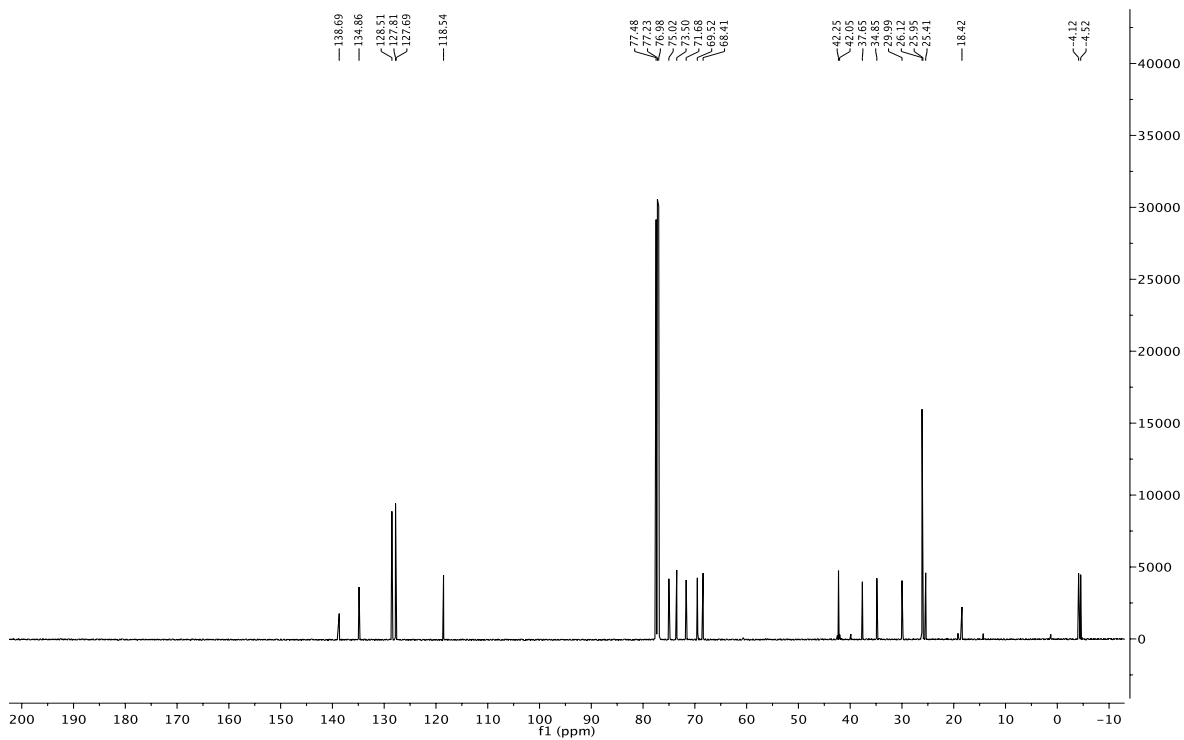
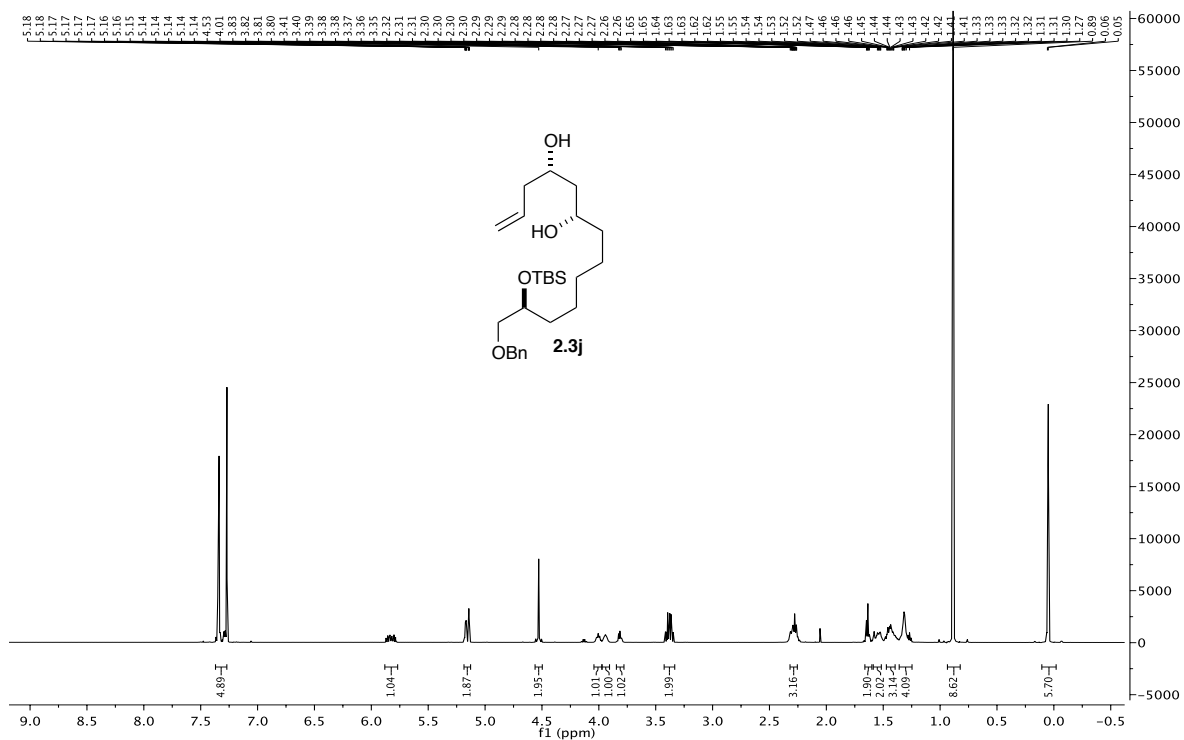
(1*R*,6*R*,8*S*)-8-((*S*)-7-(Benzyloxy)-6-((*tert*-butyldimethylsilyl)oxy)heptyl)-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-ene 1-oxide (2.3i) (Chapter-2):



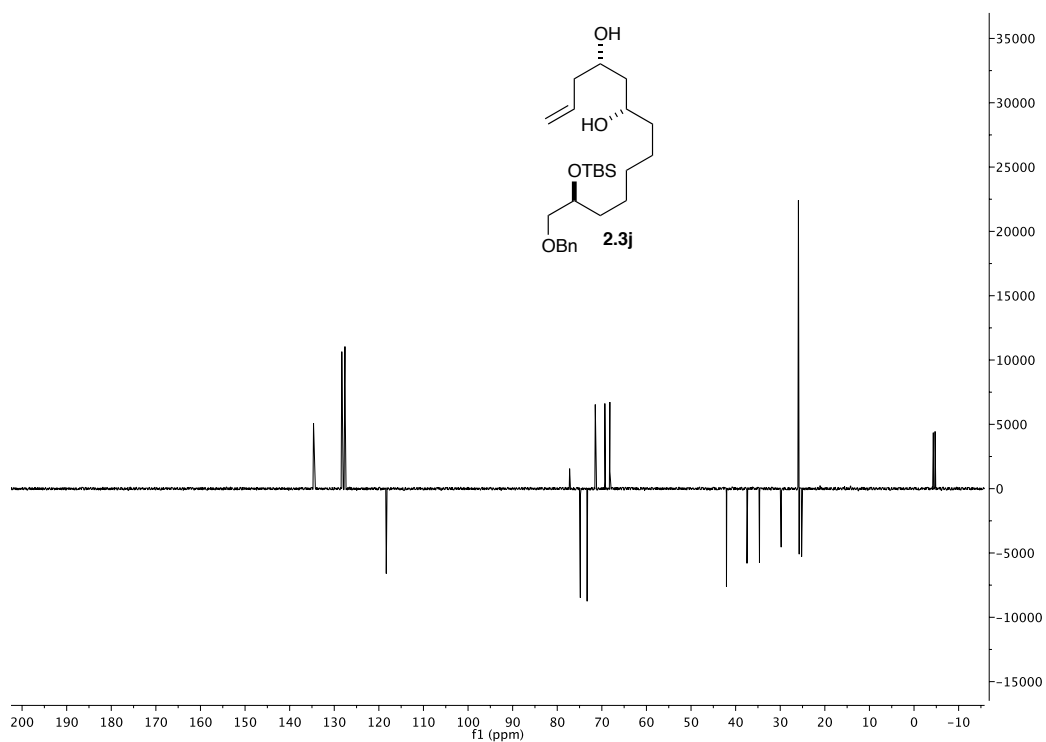
(1*R*,6*R*,8*S*)-8-((*S*)-7-(Benzyloxy)-6-((*tert*-butyldimethylsilyl)oxy)heptyl)-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-ene 1-oxide (2.3i):



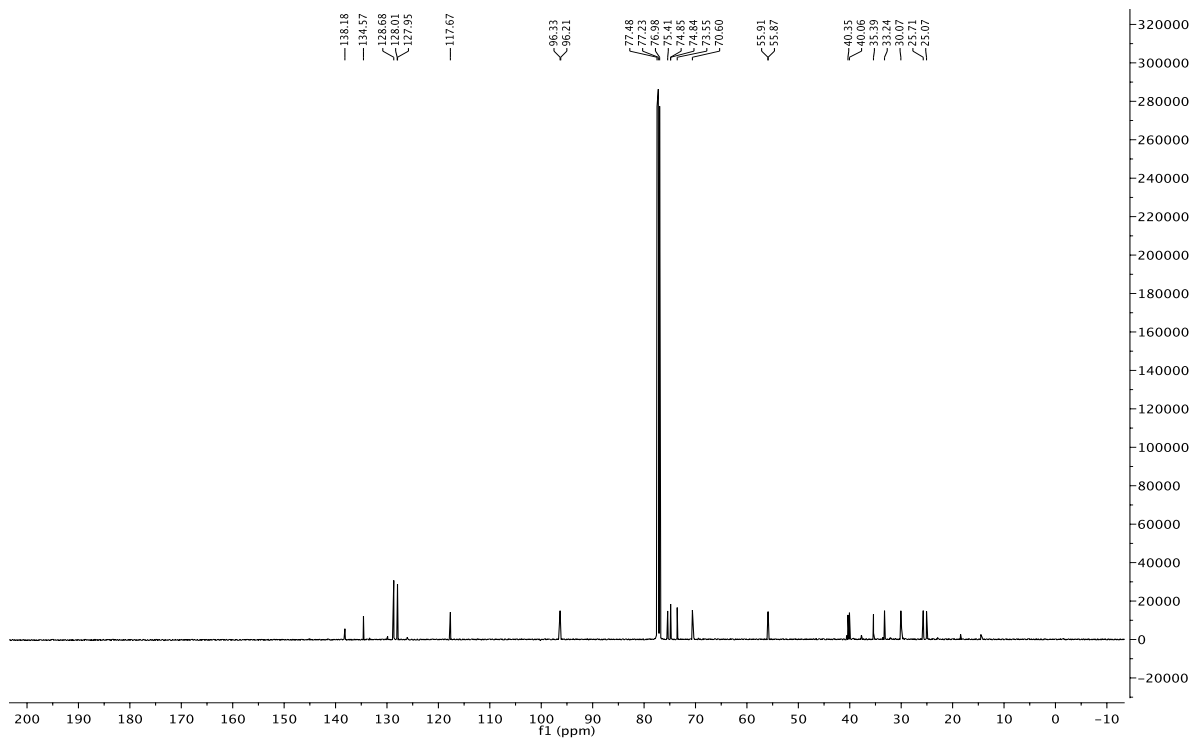
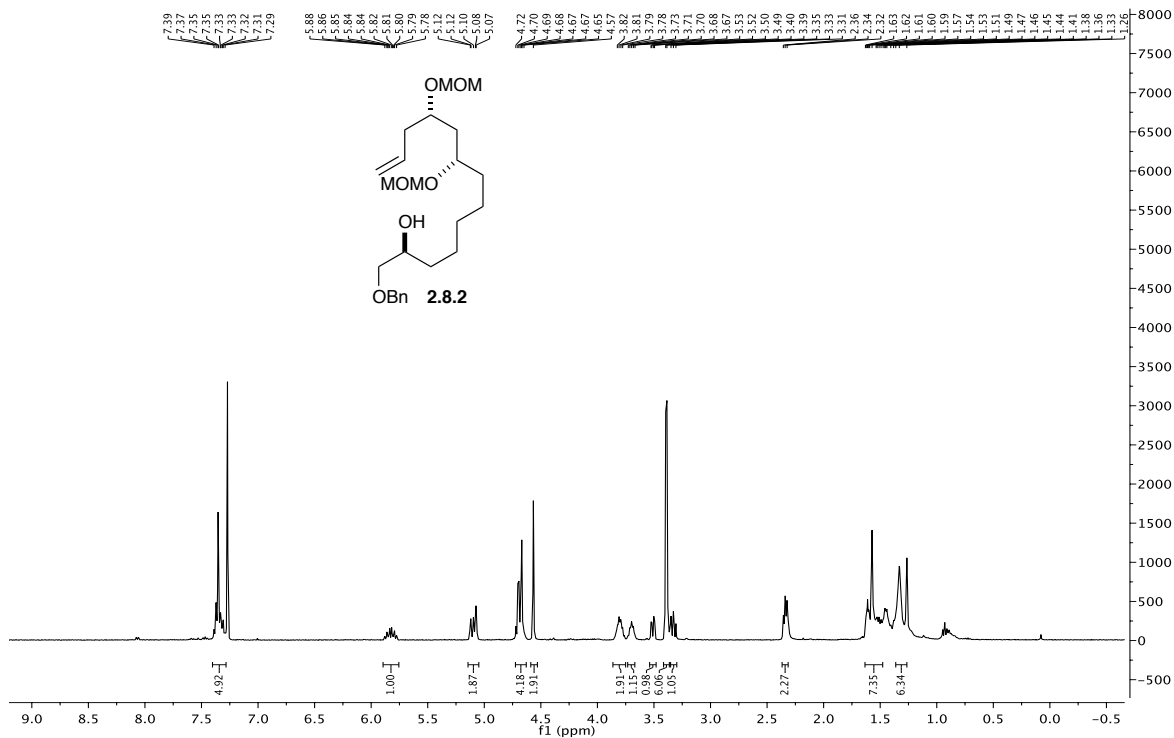
**(4*S*,6*S*,12*S*)-13-(Benzyloxy)-12-((*tert*-butyldimethylsilyl)oxy)tridec-1-ene-4,6-diol
(2.3j):**



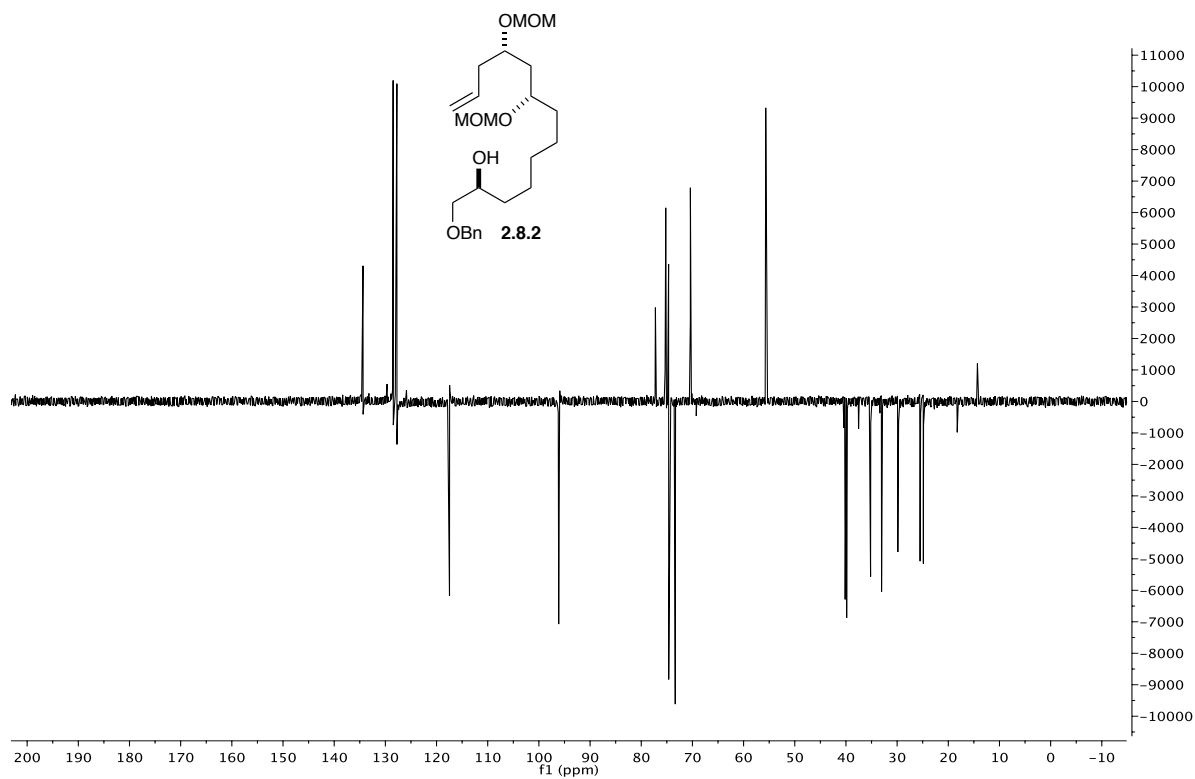
**(4*S*,6*S*,12*S*)-13-(Benzyloxy)-12-((*tert*-butyldimethylsilyl)oxy)tridec-1-ene-4,6-diol
(2.3j):**



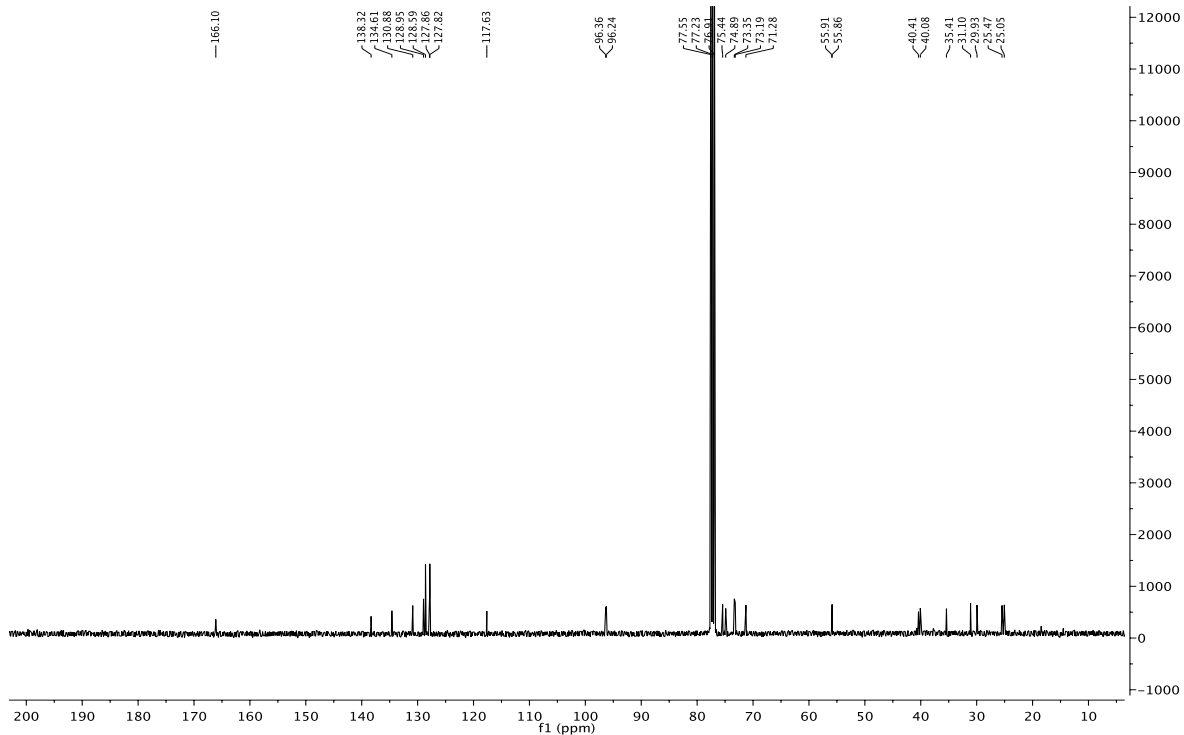
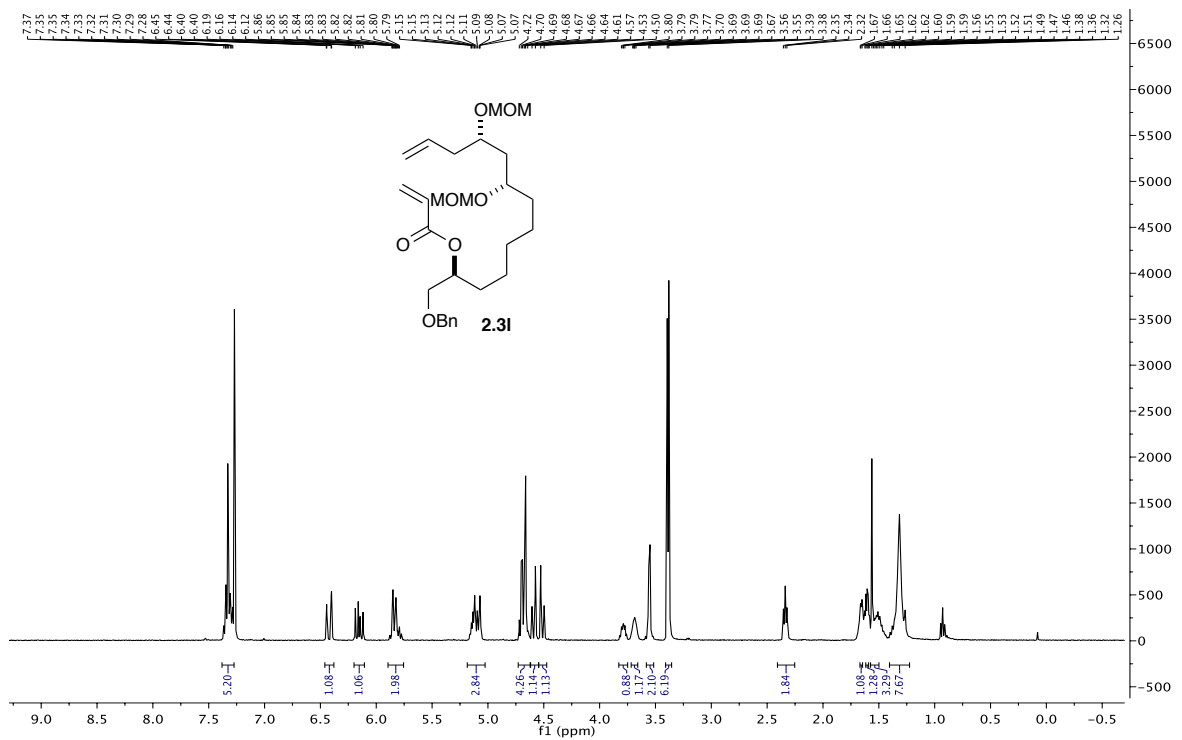
(2*S*,8*S*,10*S*)-1-(Benzyloxy)-8,10-bis(methoxymethoxy)tridec-12-en-2-ol (2.8.2):



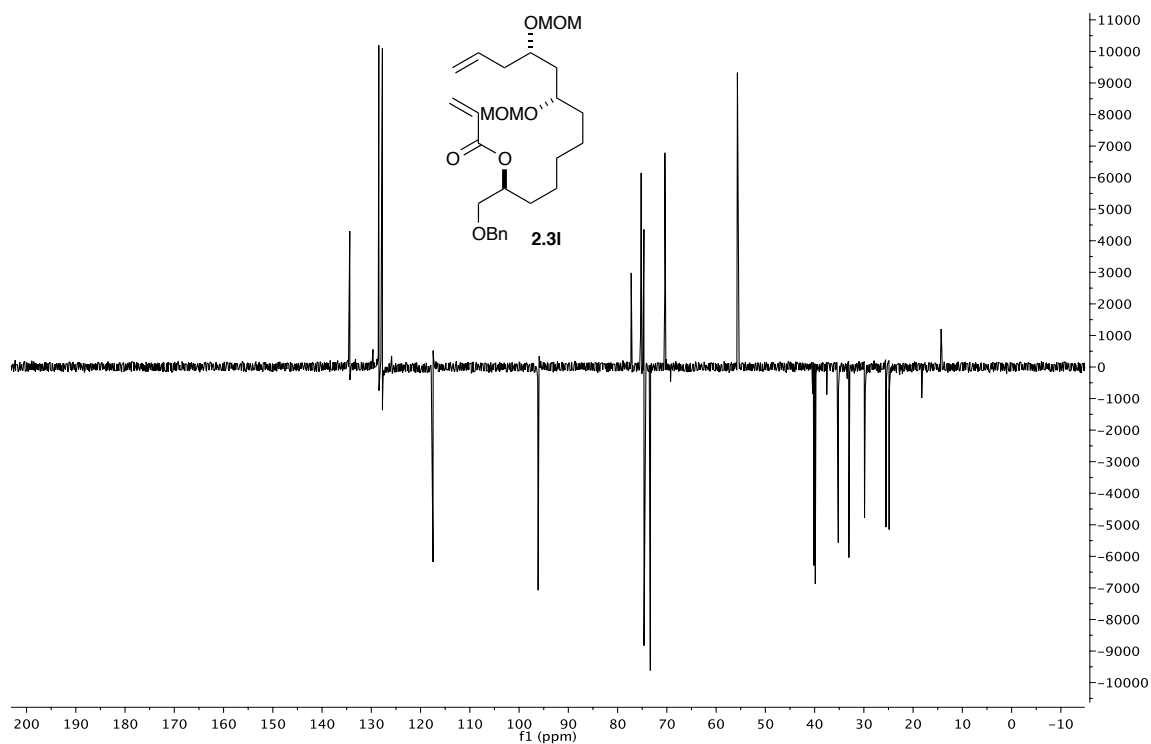
(2*S*,8*S*,10*S*)-1-(Benzyloxy)-8,10-bis(methoxymethoxy)tridec-12-en-2-ol (2.8.2):



**(2*S*,8*S*,10*S*)-1-(Benzyloxy)-8,10-bis(methoxymethoxy)tridec-12-en-2-yl acrylate
(2.3I):**



**(2*S*,8*S*,10*S*)-1-(Benzyloxy)-8,10-bis(methoxymethoxy)tridec-12-en-2-yl acrylate
(2.3I):**



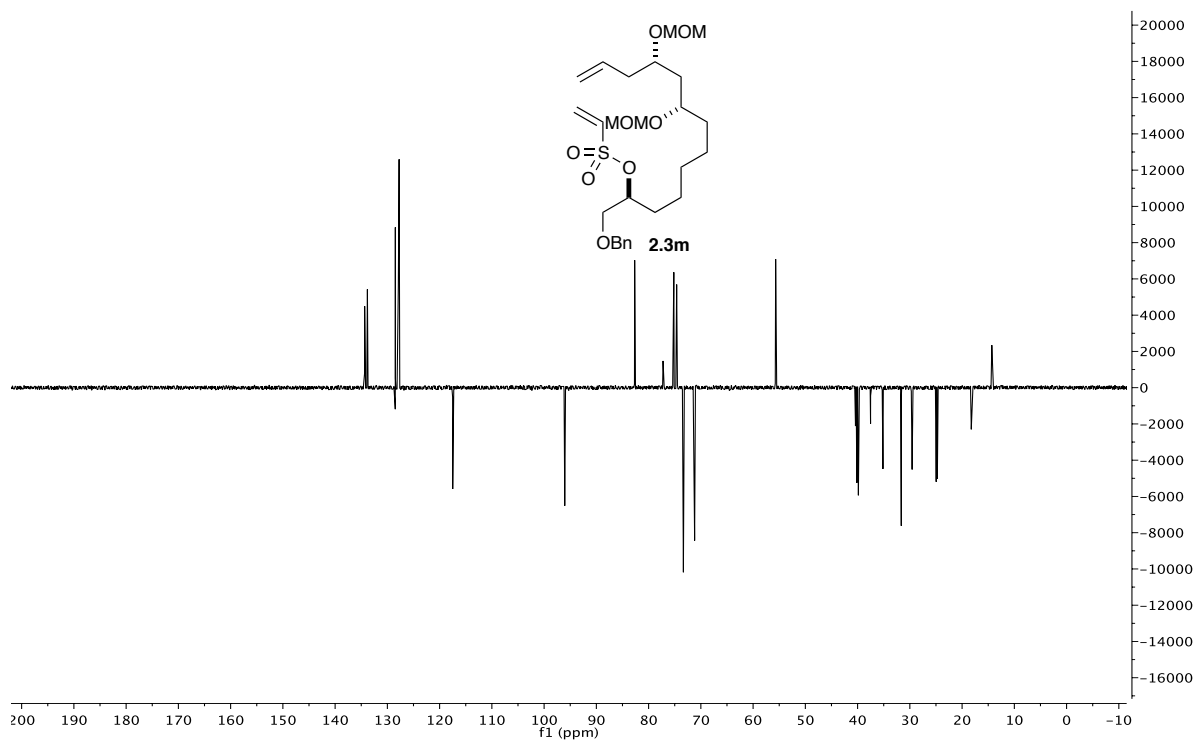
Chemical structure of compound **2.3m** is shown above the spectrum. The structure is a 10-membered ring containing a sulfonate group (OMOM) and a benzyloxy group (OBn). The ring also has a vinyl group and a methyl group.

¹H NMR spectrum (CDCl₃) of compound **2.3m**. The x-axis represents the chemical shift in ppm (f1), ranging from 9.0 to -0.5. The y-axis represents the intensity, ranging from 0 to 17000. The spectrum shows several peaks, with integration values provided below the baseline.

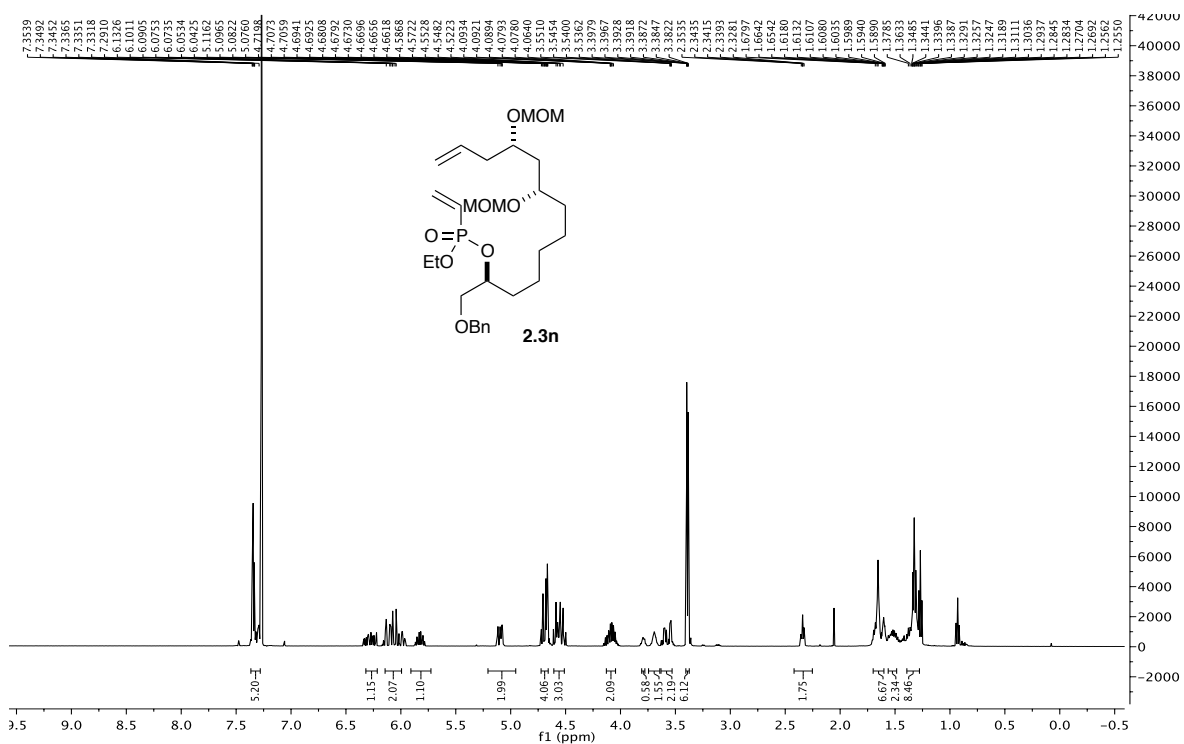
Integration values (from left to right): 4.99, 1.00, 1.02, 1.01, 0.96, 1.88, 5.10, 2.11, 1.05, 0.95, 1.12, 2.11, 3.05, 3.13, 1.91, 2.17, 4.19, 6.07.



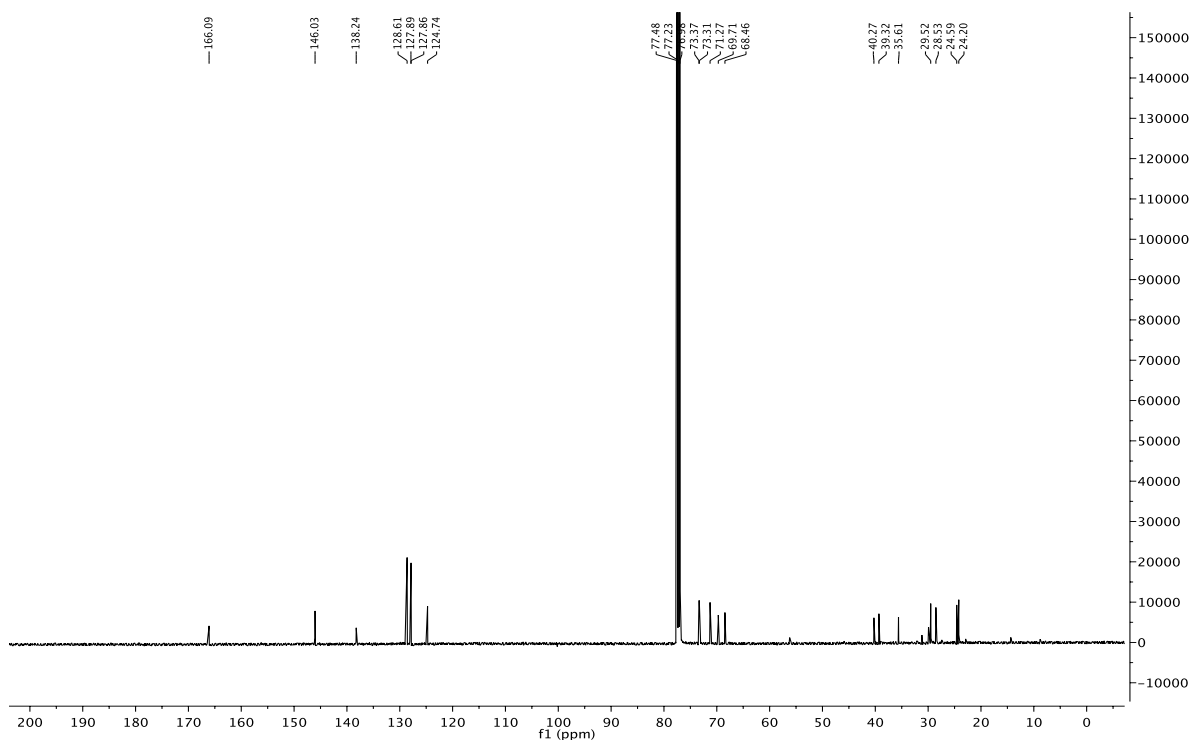
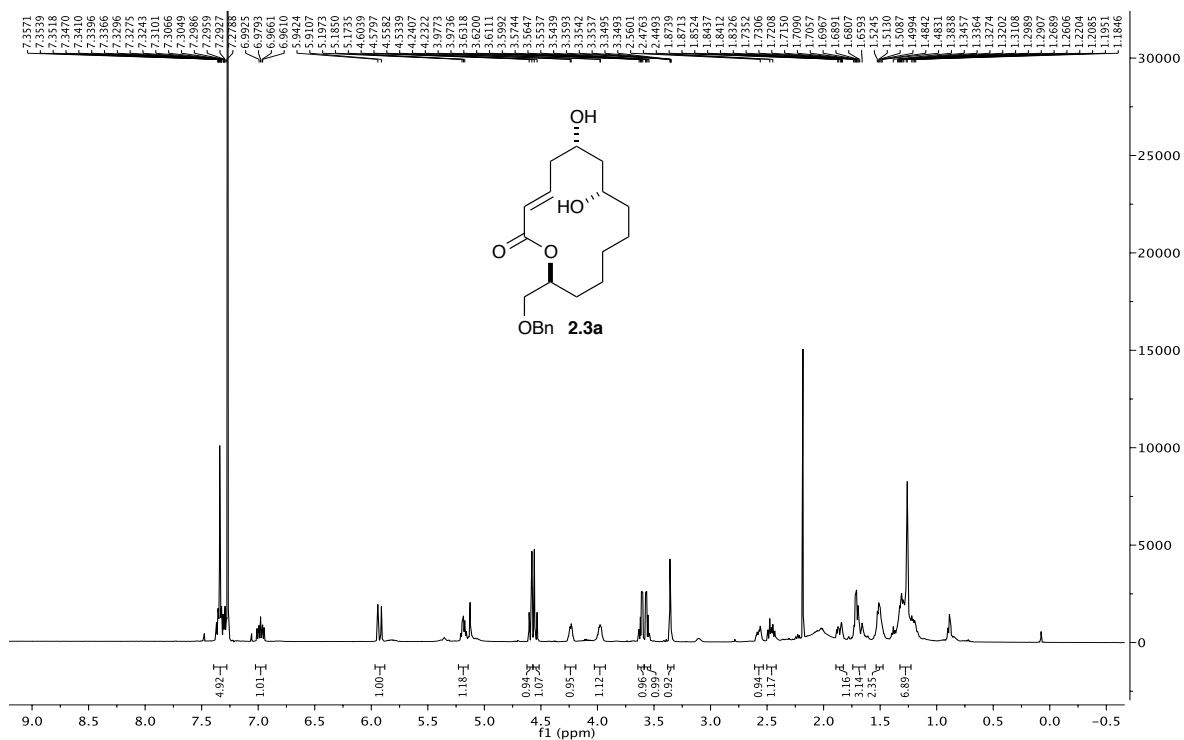
**(2*S*,8*S*,10*S*)-1-(Benzyloxy)-8,10-bis(methoxymethoxy)tridec-12-en-2-yl
ethenesulfonate (2.3m):**



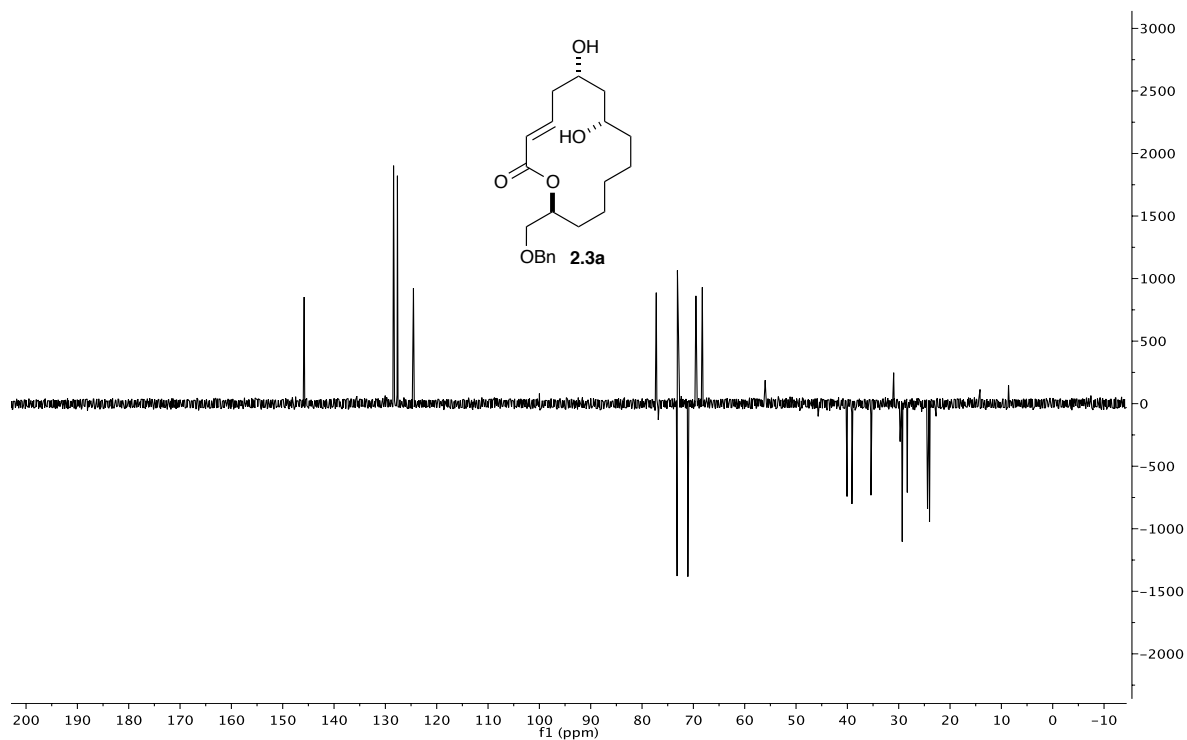
(2*S*,8*S*,10*S*)-1-(Benzyloxy)-8,10-bis(methoxymethoxy)tridec-12-en-2-yl ethyl vinylphosphonate (2.3n, *R_P* and *S_P*):



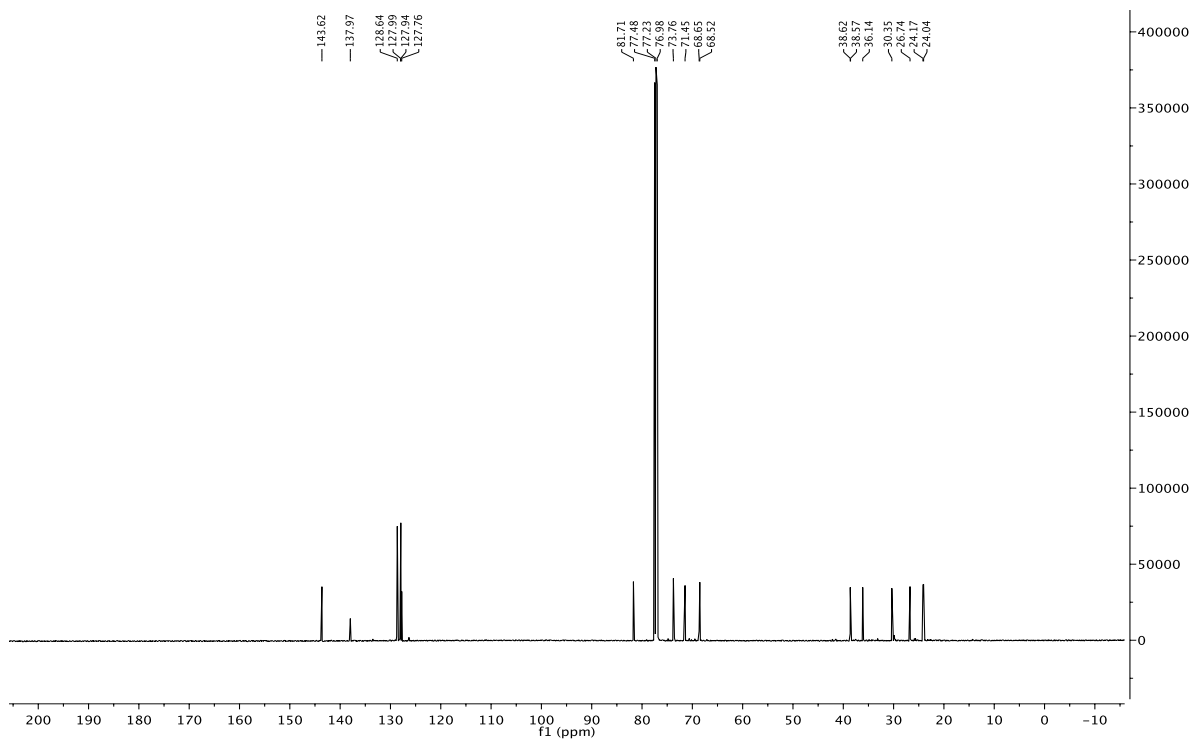
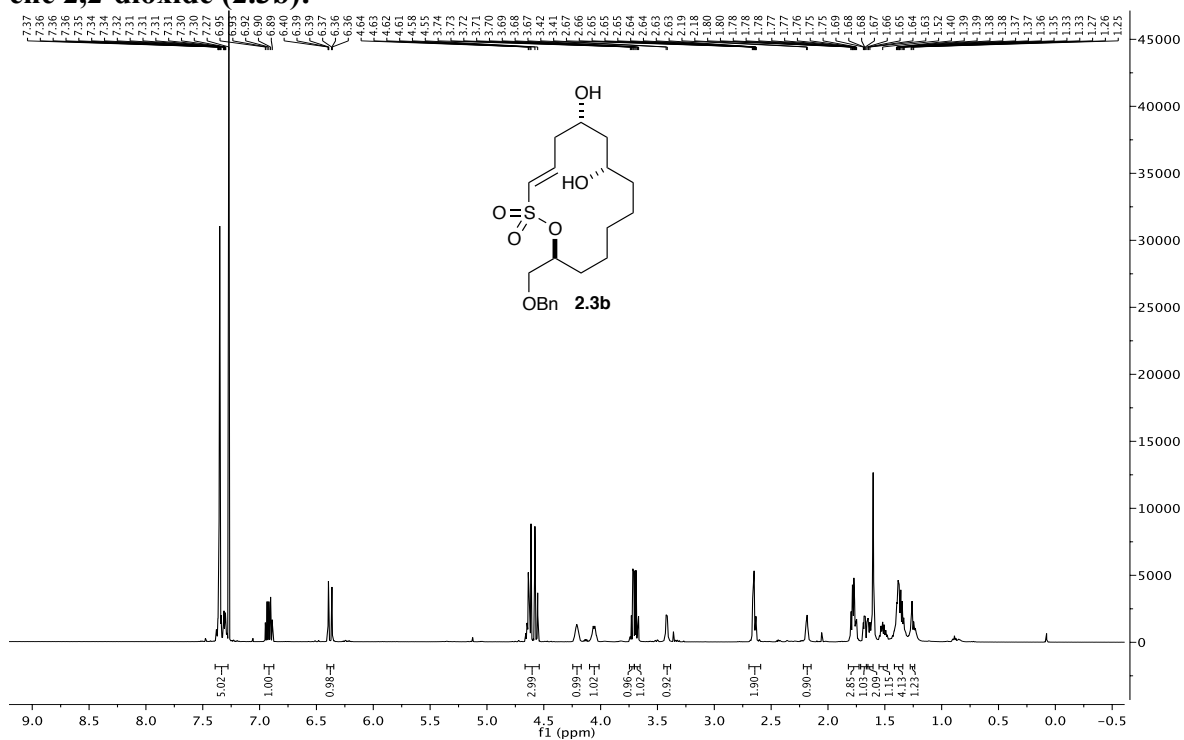
**(6*S*,8*S*,14*S*,*E*)-14-((Benzyloxy)methyl)-6,8-dihydroxyoxacyclotetradec-3-en-2-one
(2.3a):**



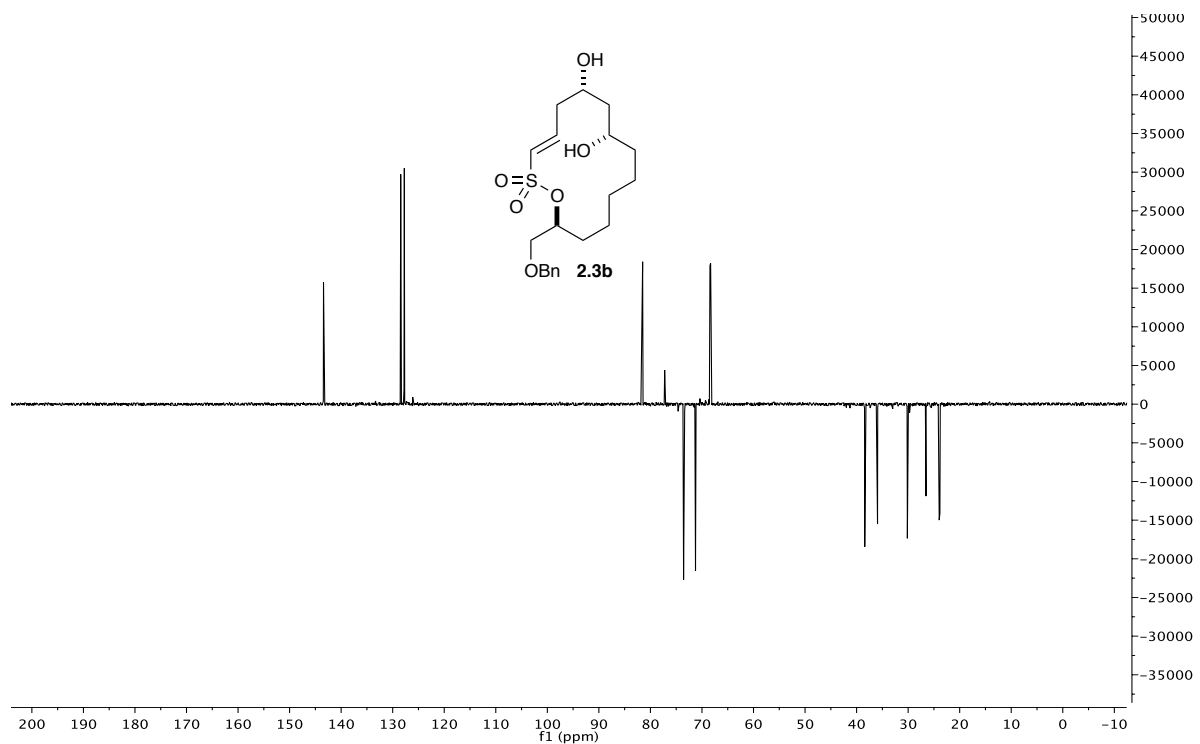
**(6*S*,8*S*,14*S*,*E*)-14-((Benzyloxy)methyl)-6,8-dihydroxyoxacyclotetradec-3-en-2-one
(2.3a):**



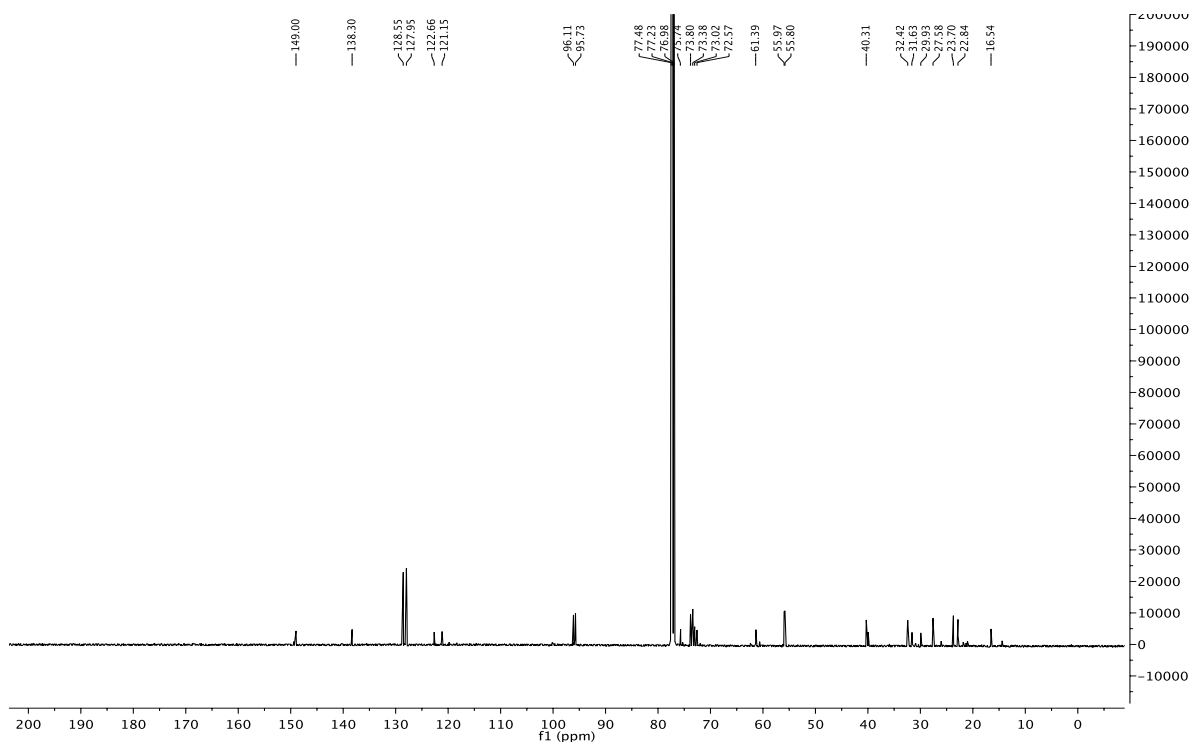
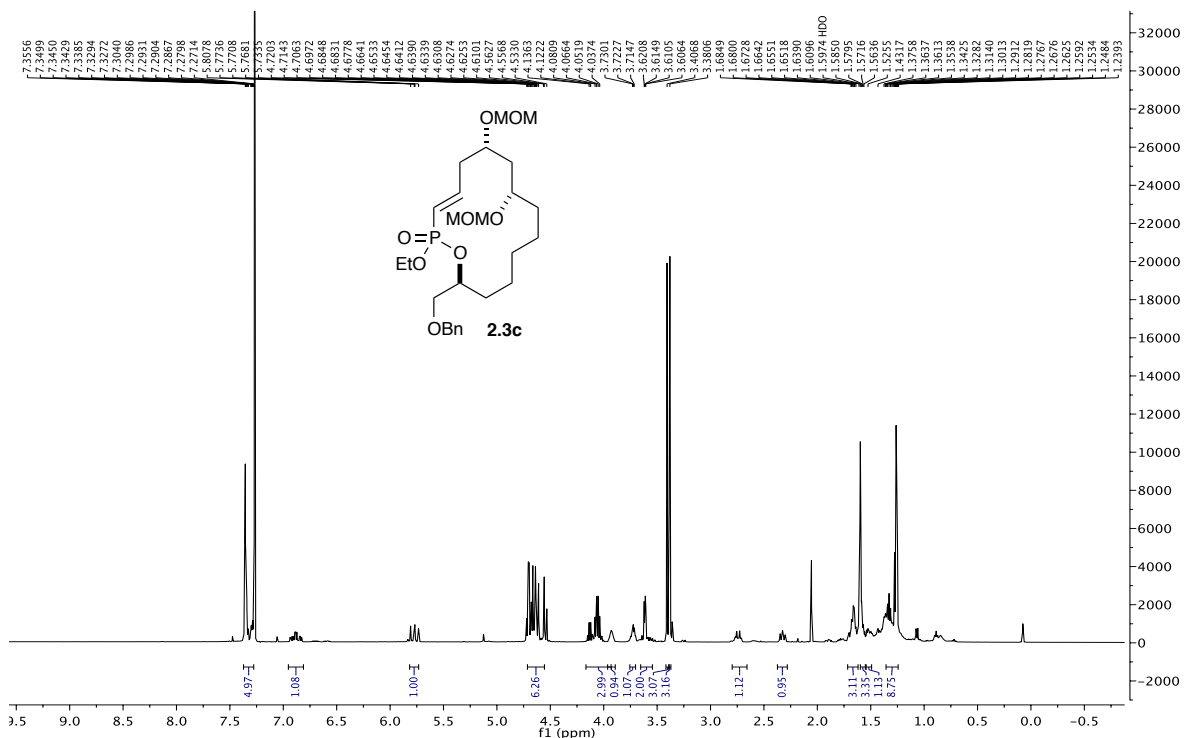
(6*S*,8*S*,14*S*,*E*)-14-((Benzyloxy)methyl)-6,8-dihydroxy-1-oxa-2-thiacyclotetradec-3-ene 2,2-dioxide (2.3b):



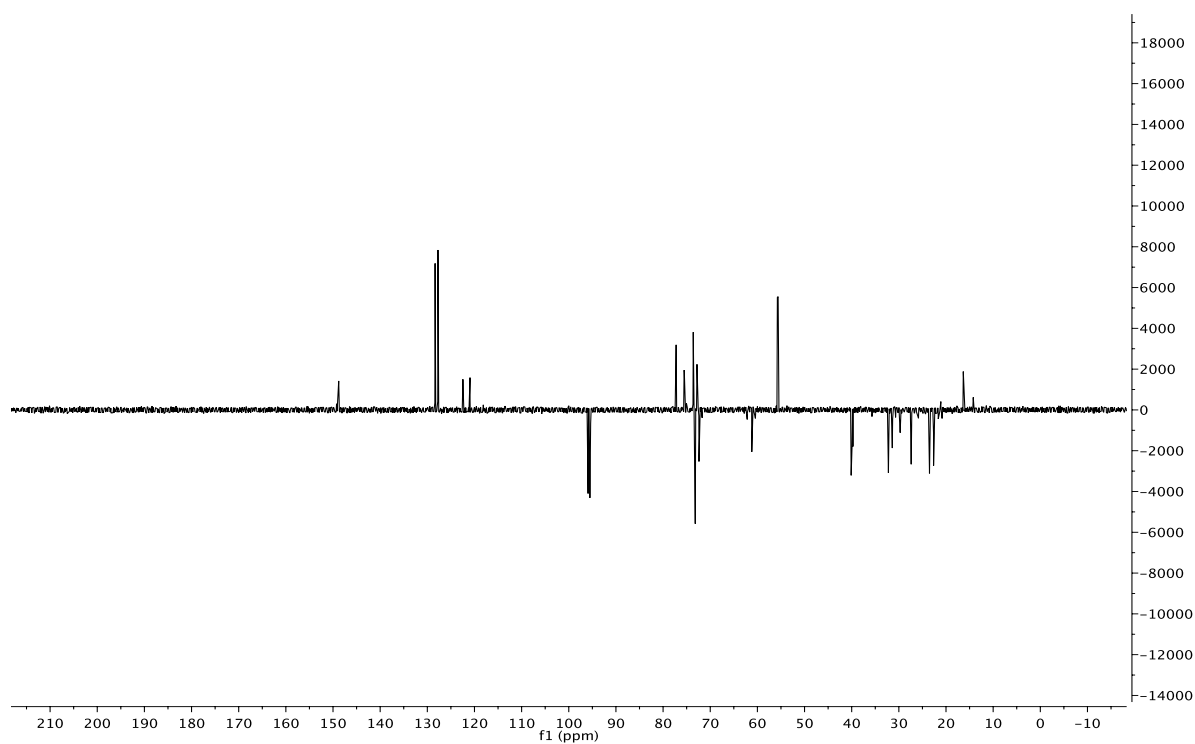
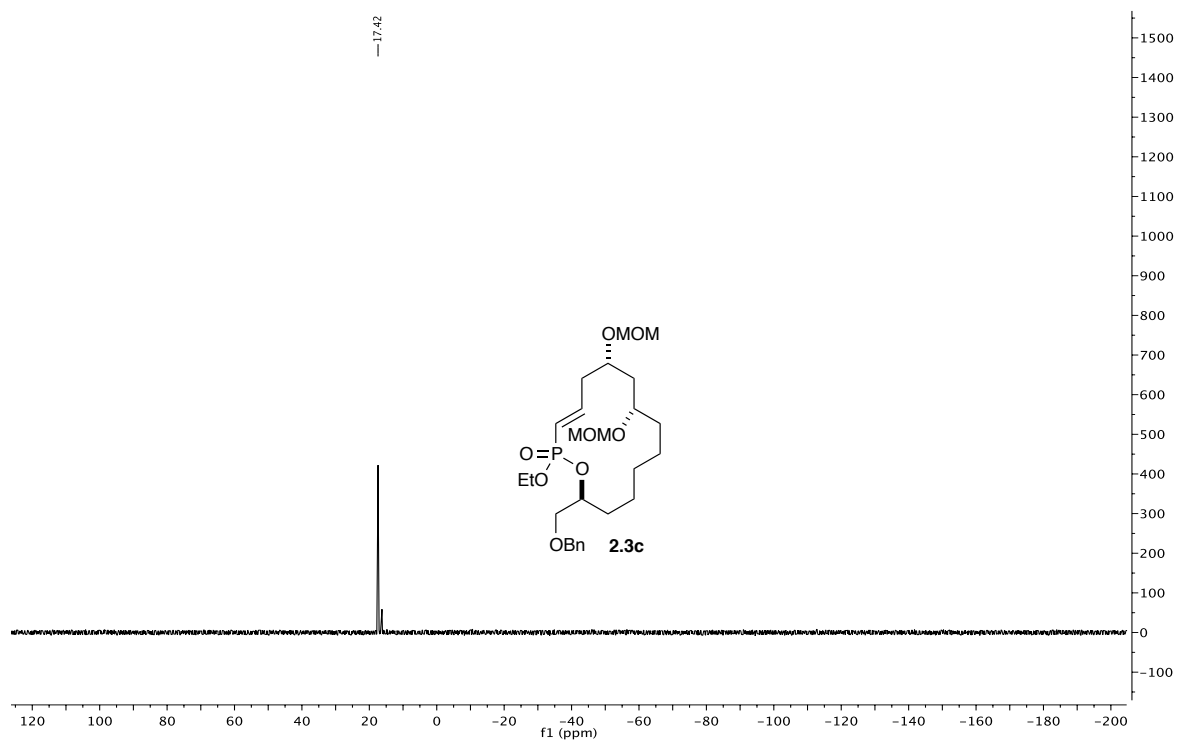
(6*S*,8*S*,14*S*,*E*)-14-((Benzyloxy)methyl)-6,8-dihydroxy-1-oxa-2-thiacyclotetradec-3-ene 2,2-dioxide (2.3b):



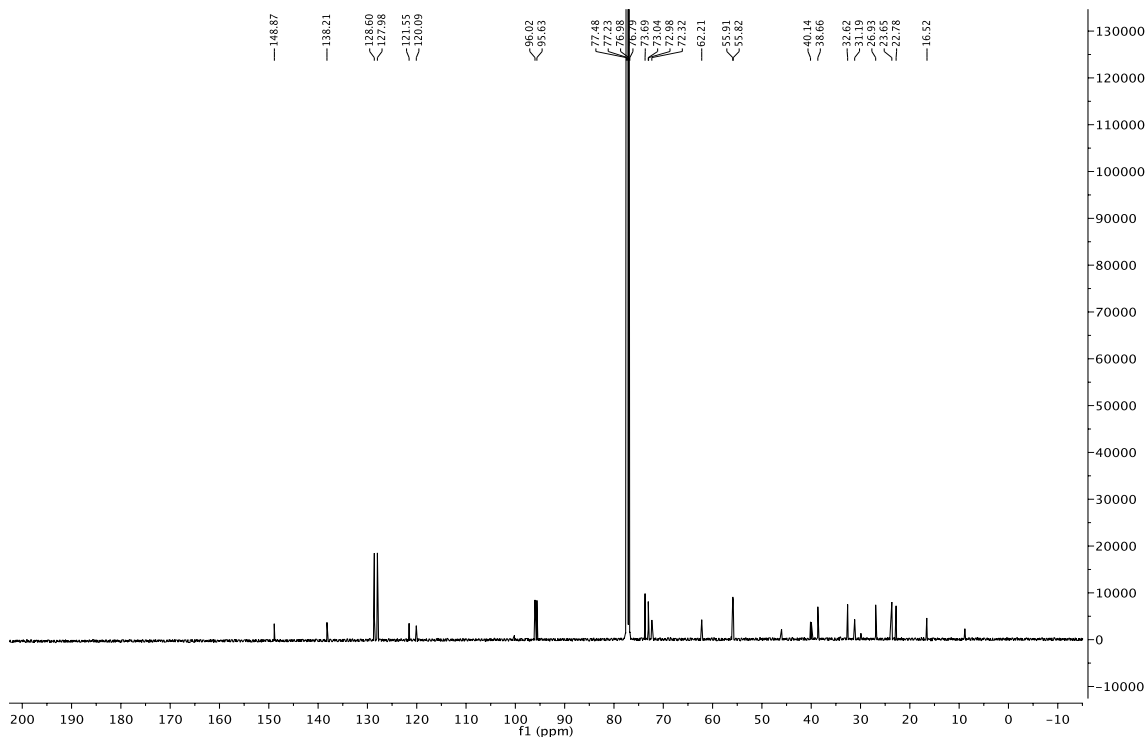
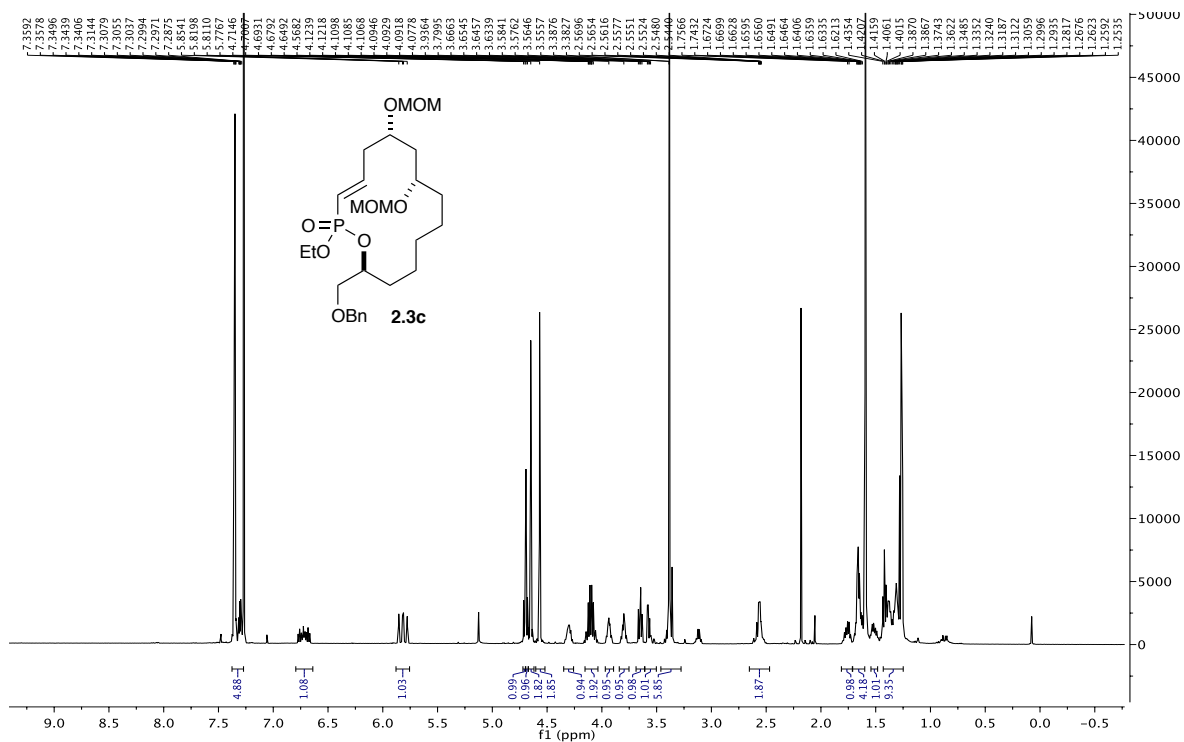
(6*S*,8*S*,14*S*,*E*)-14-((Benzyloxy)methyl)-6,8-bis(methoxymethoxy)-1-oxa-2-thiacyclotetradec-3-ene 2,2-dioxide [Diastereomer-1, 2.3c, (*R_P* and *S_P*)]:



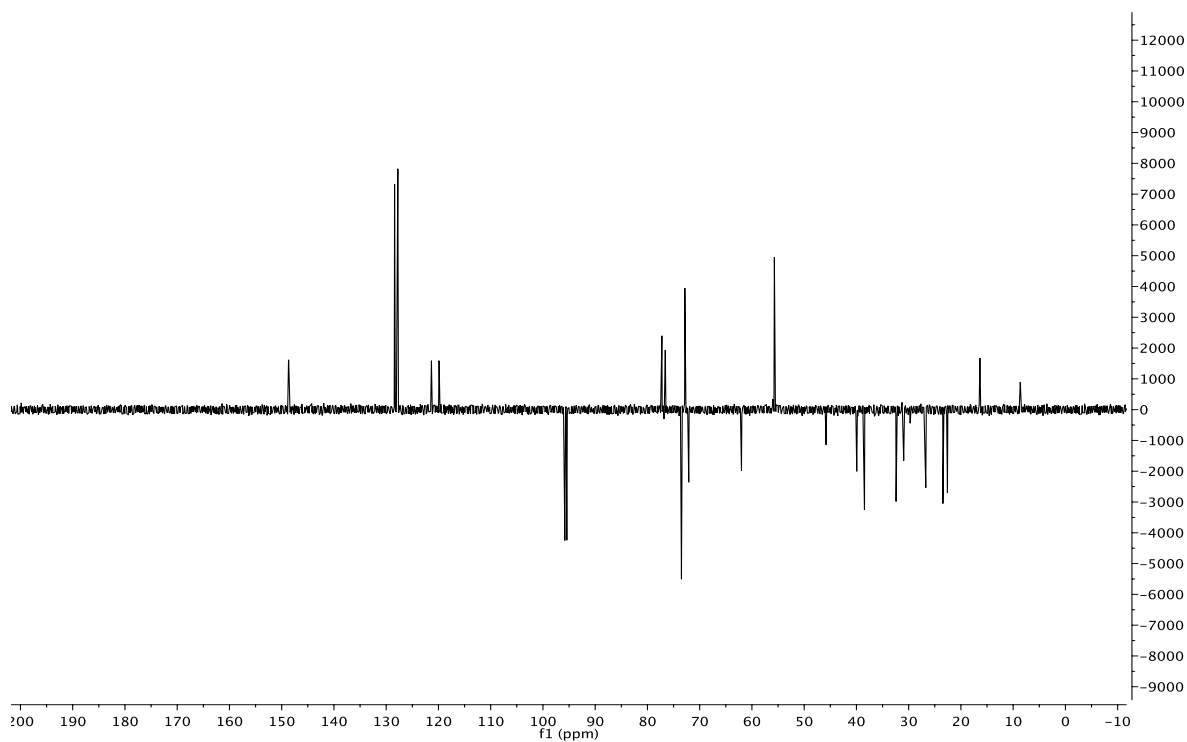
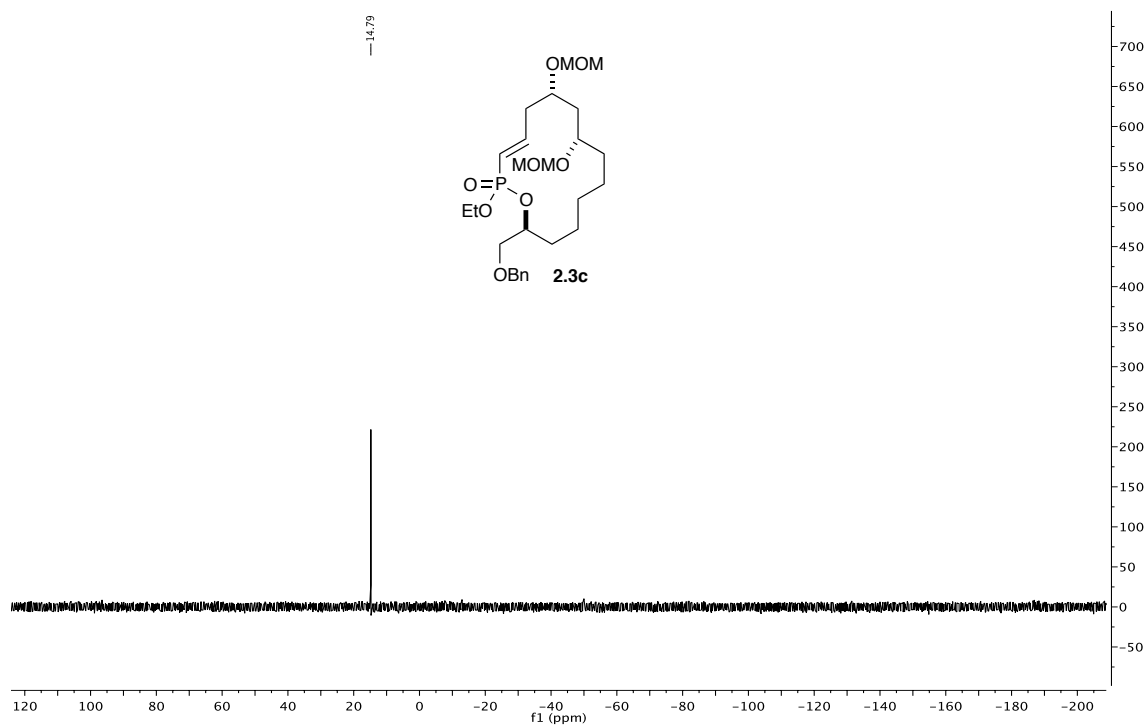
(6*S*,8*S*,14*S*,*E*)-14-((Benzyloxy)methyl)-6,8-bis(methoxymethoxy)-1-oxa-2-thiacyclotetradec-3-ene 2,2-dioxide [Diastereomer-1, 2.3c, (*R_P* and *S_P*)]:



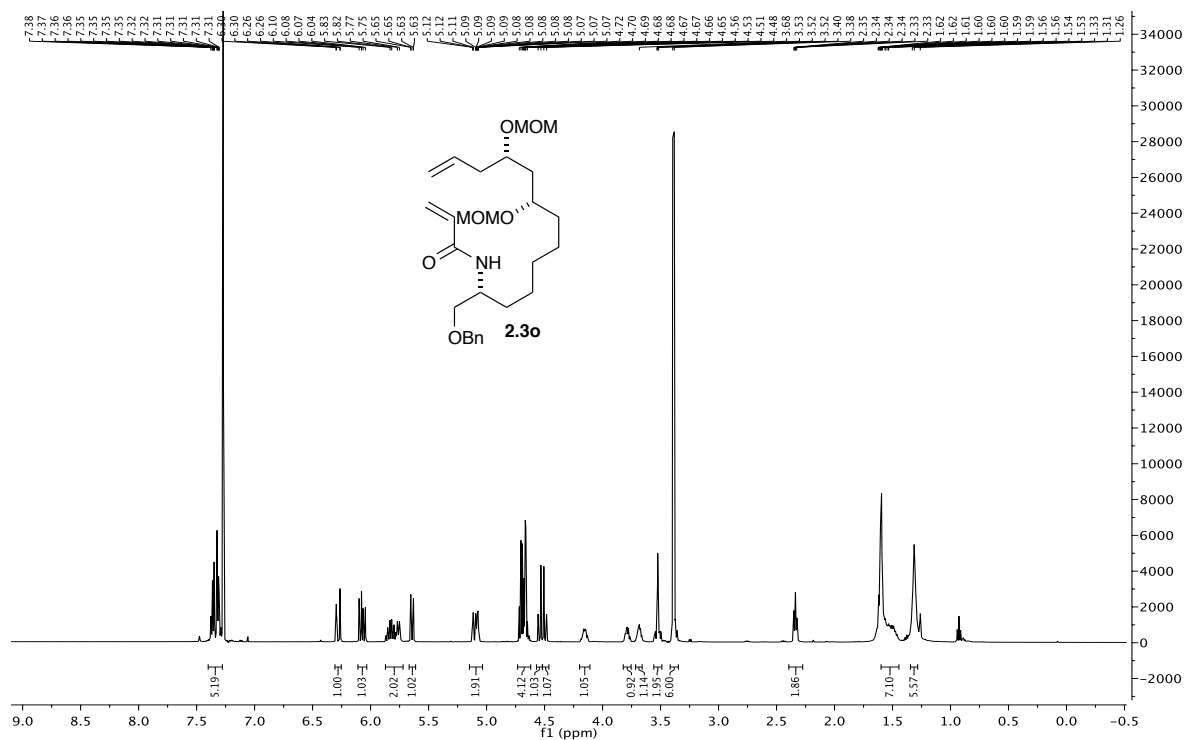
(6*S*,8*S*,14*S*,*E*)-14-((Benzyloxy)methyl)-6,8-bis(methoxymethoxy)-1-oxa-2-thiacyclotetradec-3-ene 2,2-dioxide [Diastereomer-2, 2.3c, (*R_P* and *S_P*)]:



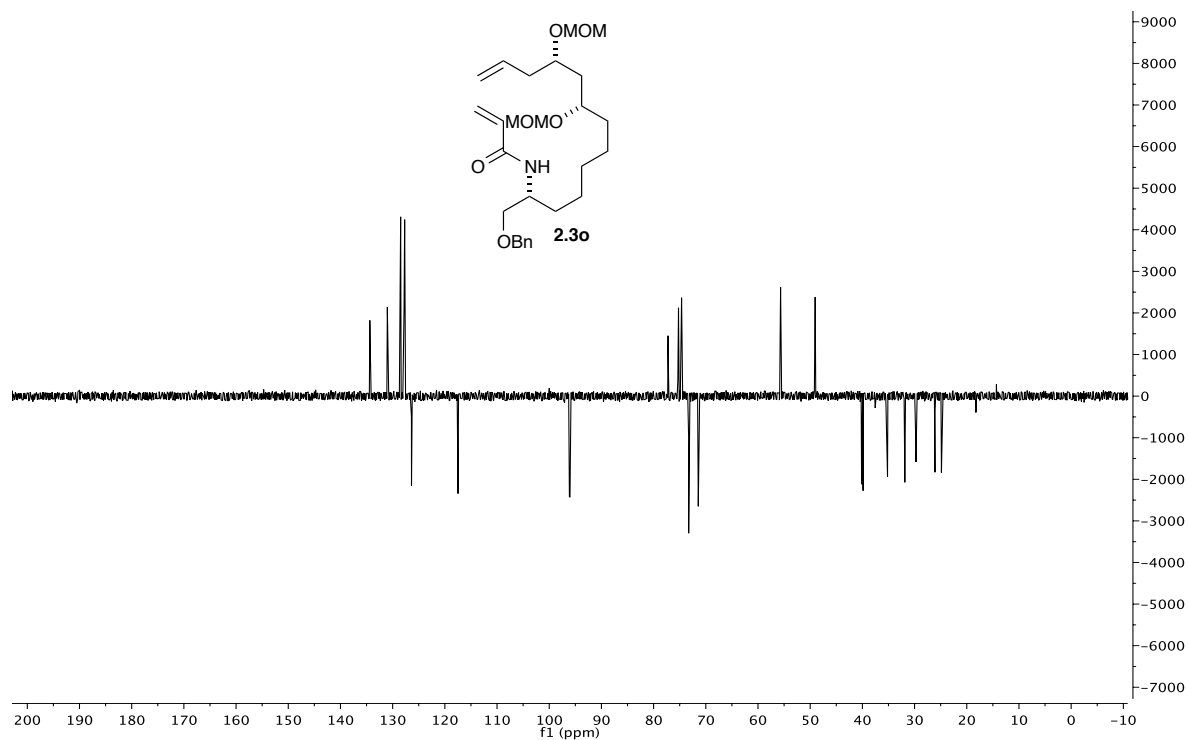
(6*S*,8*S*,14*S*,*E*)-14-((Benzyloxy)methyl)-6,8-bis(methoxymethoxy)-1-oxa-2-thiacyclotetradec-3-ene 2,2-dioxide [Diastereomer-2, 2.3c, (*R_P* and *S_P*)]:



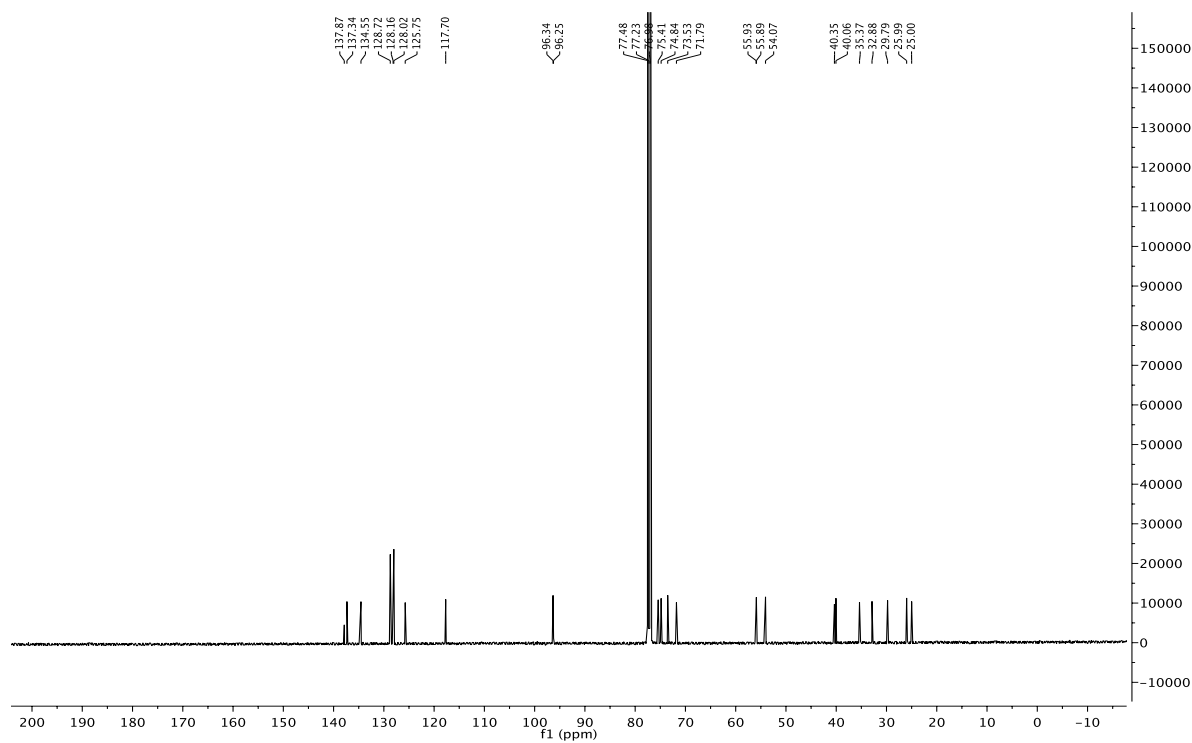
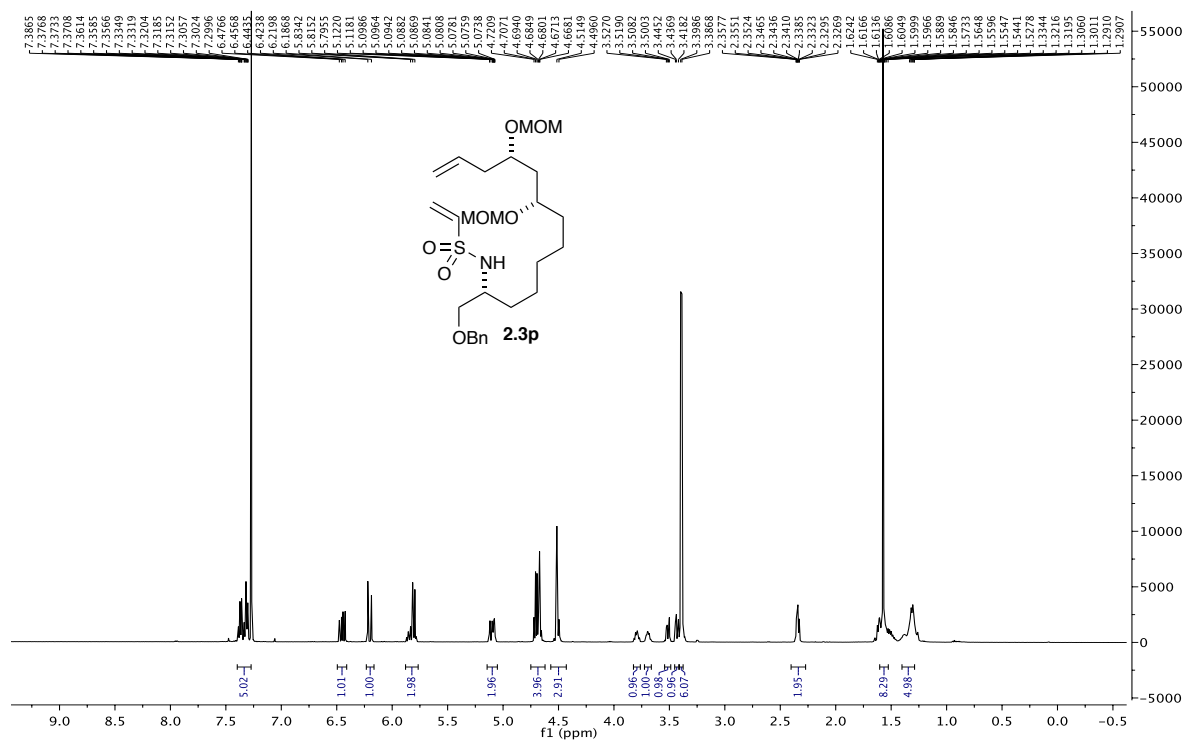
***N*-((2*R*,8*S*,10*S*)-1-(Benzyloxy)-8,10-bis(methoxymethoxy)tridec-12-en-2-yl)-acrylamide (2.3o):**



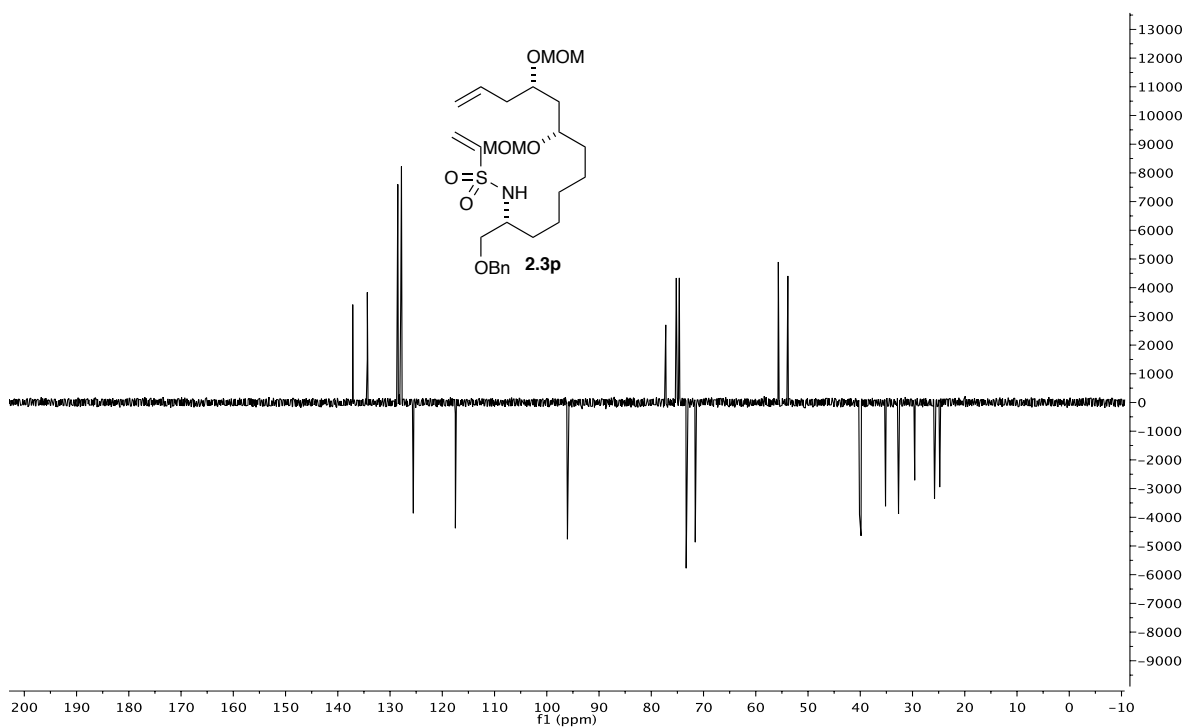
***N*-((2*R*,8*S*,10*S*)-1-(Benzyloxy)-8,10-bis(methoxymethoxy)tridec-12-en-2-yl)-acrylamide (2.3o):**



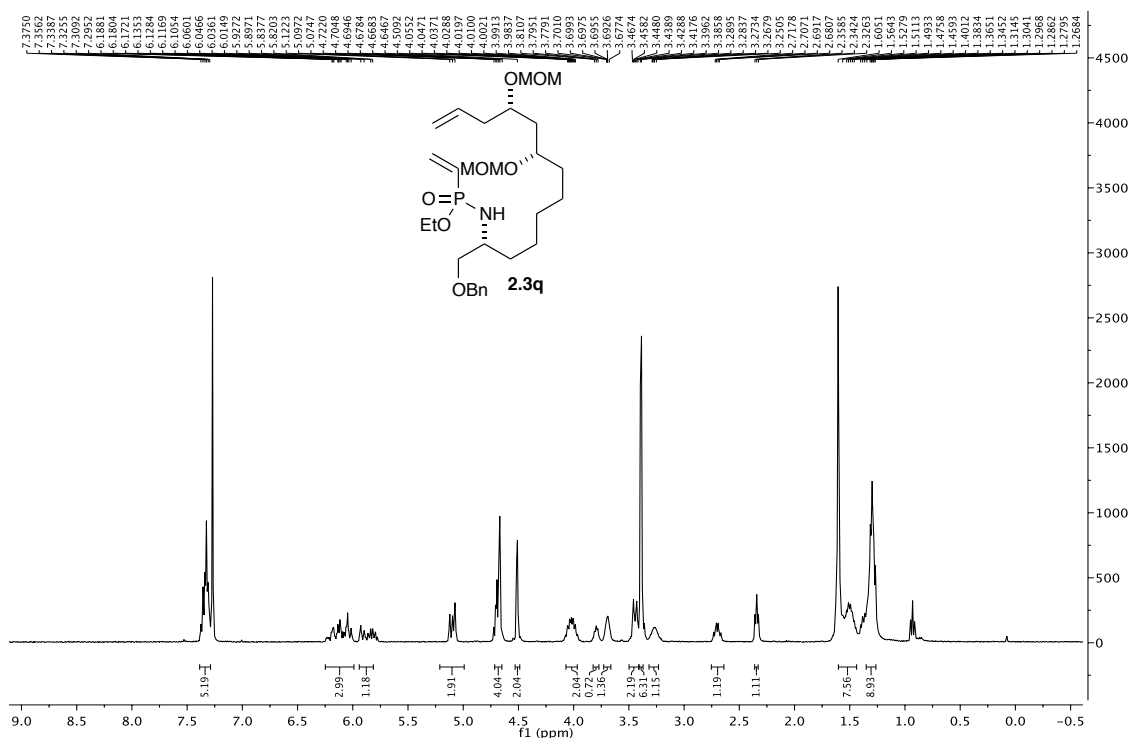
***N*-((2*R*,8*S*,10*S*)-1-(Benzyloxy)-8,10-bis(methoxymethoxy)tridec-12-en-2-yl)ethanesulfonamide (2.3p):**



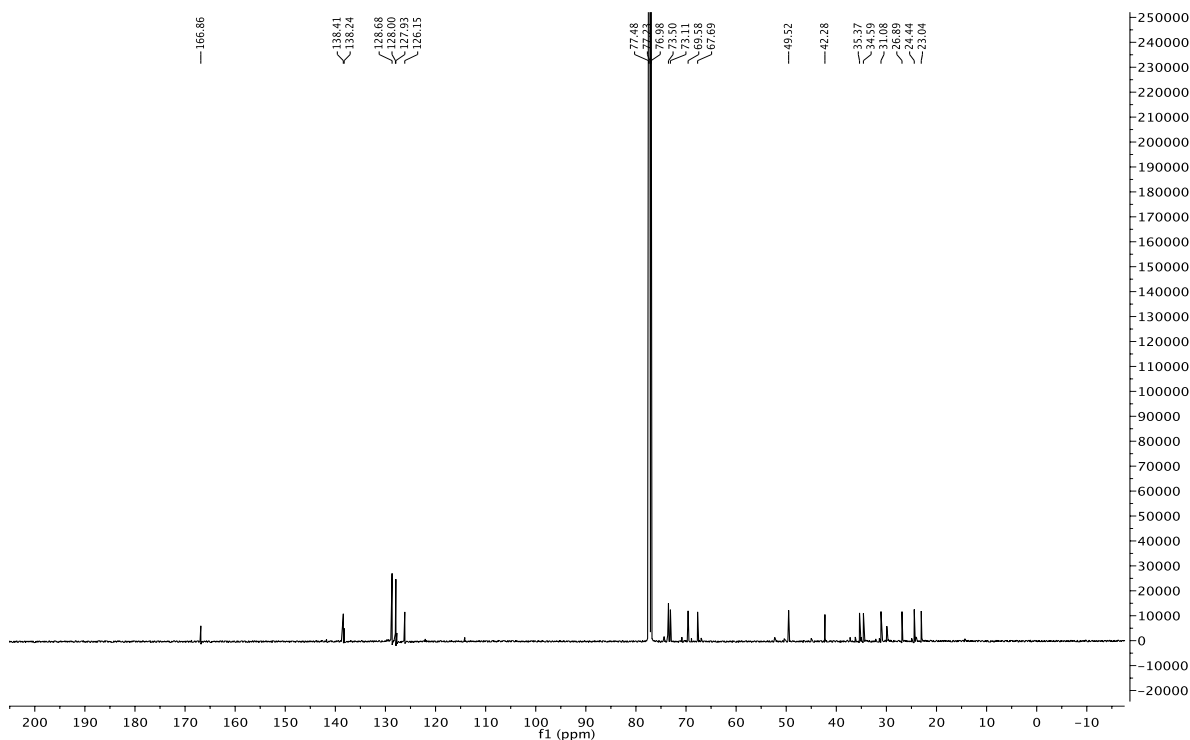
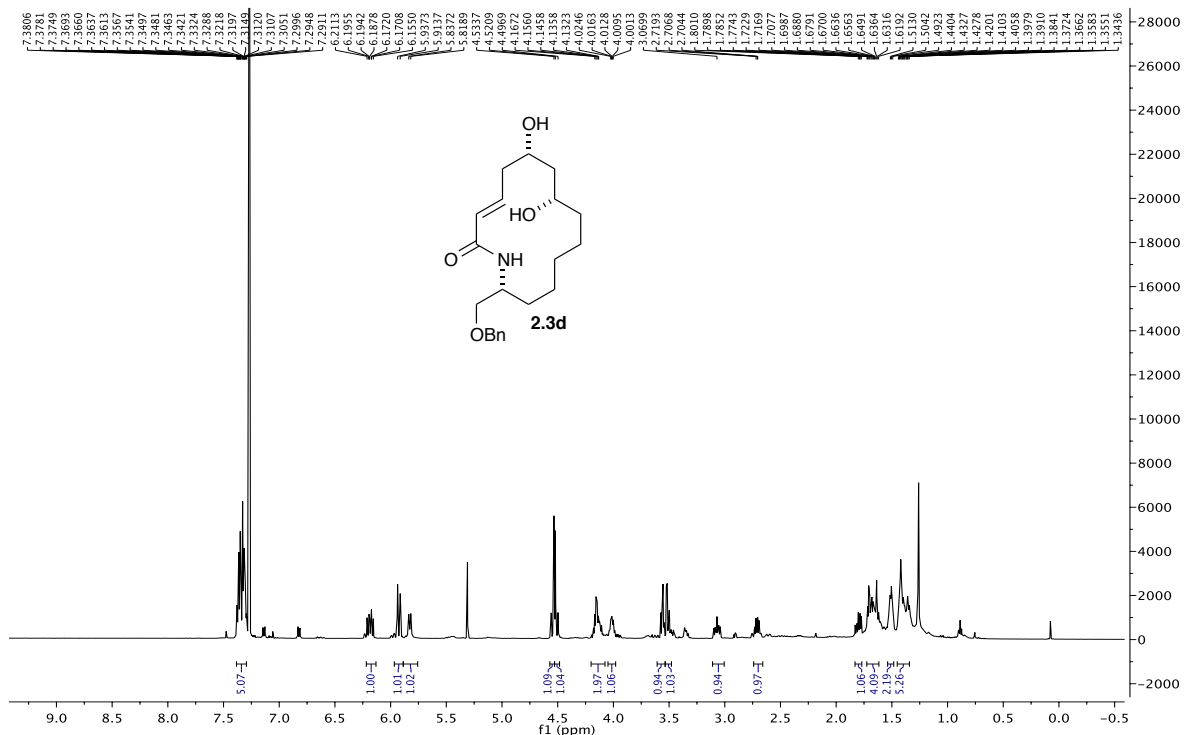
***N*-((2*R*,8*S*,10*S*)-1-(Benzyloxy)-8,10-bis(methoxymethoxy)tridec-12-en-2-yl)ethanesulfonamide (2.3p):**



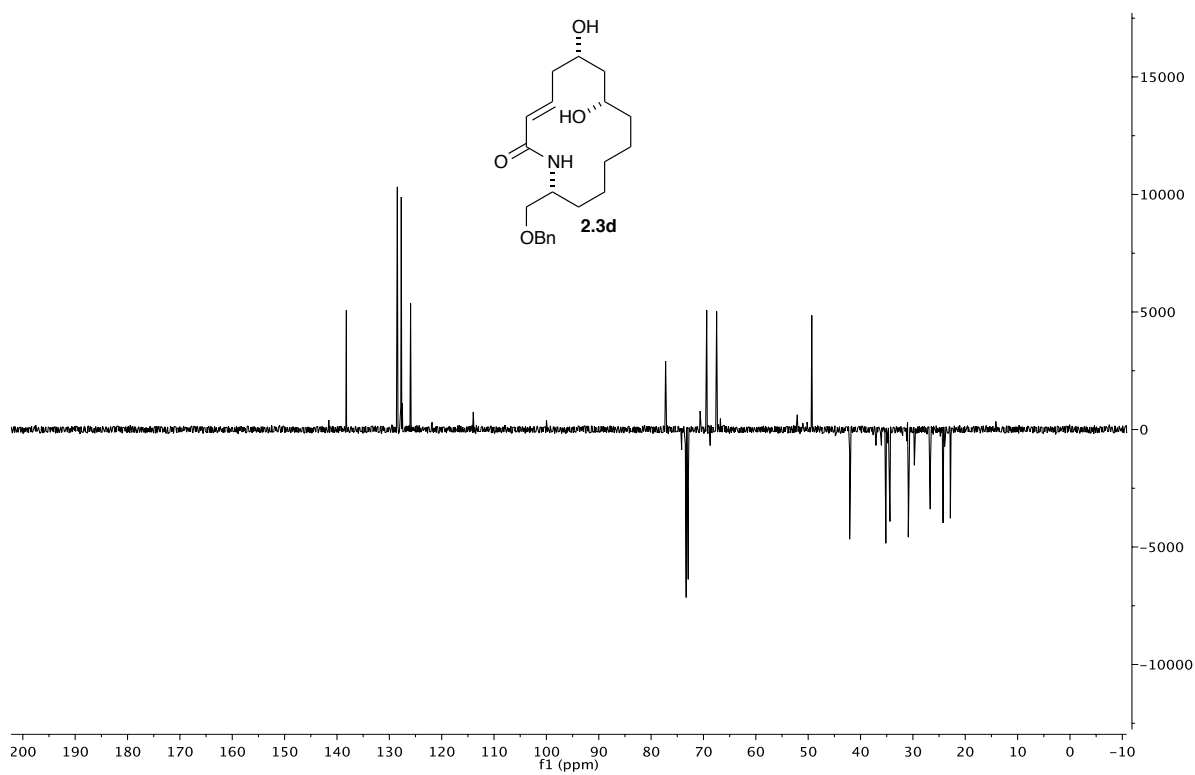
Ethyl*N*-((2*R*,8*S*,10*S*)-1-(benzyloxy)-8,10-bis(methoxymethoxy)tridec-12-en-2-yl)-*P*-vinylphosphonamidate (2.3q, *R_P* and *S_P*):



**(6*S*,8*S*,14*R*,*E*)-14-((Benzyloxy)methyl)-6,8-dihydroxyazacyclotetradec-3-en-2-one
(2.3d):**



**(6*S*,8*S*,14*R*,*E*)-14-((Benzyloxy)methyl)-6,8-dihydroxyazacyclotetradec-3-en-2-one
(2.3d):**

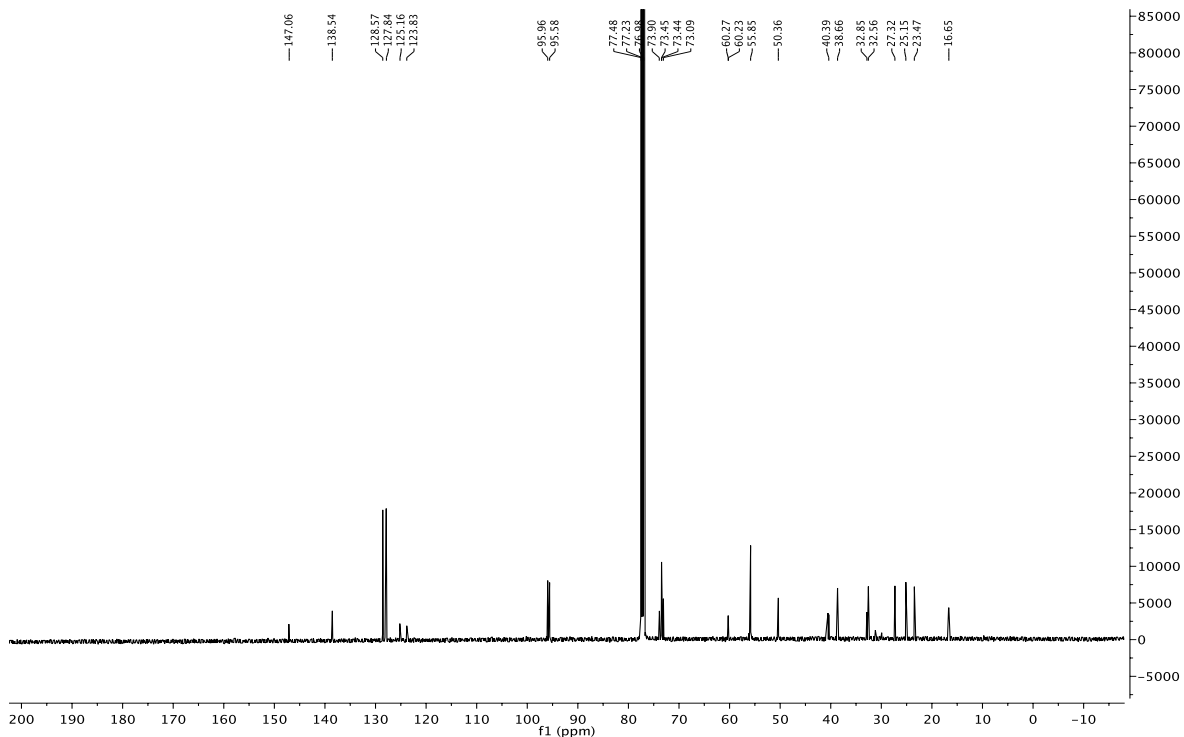
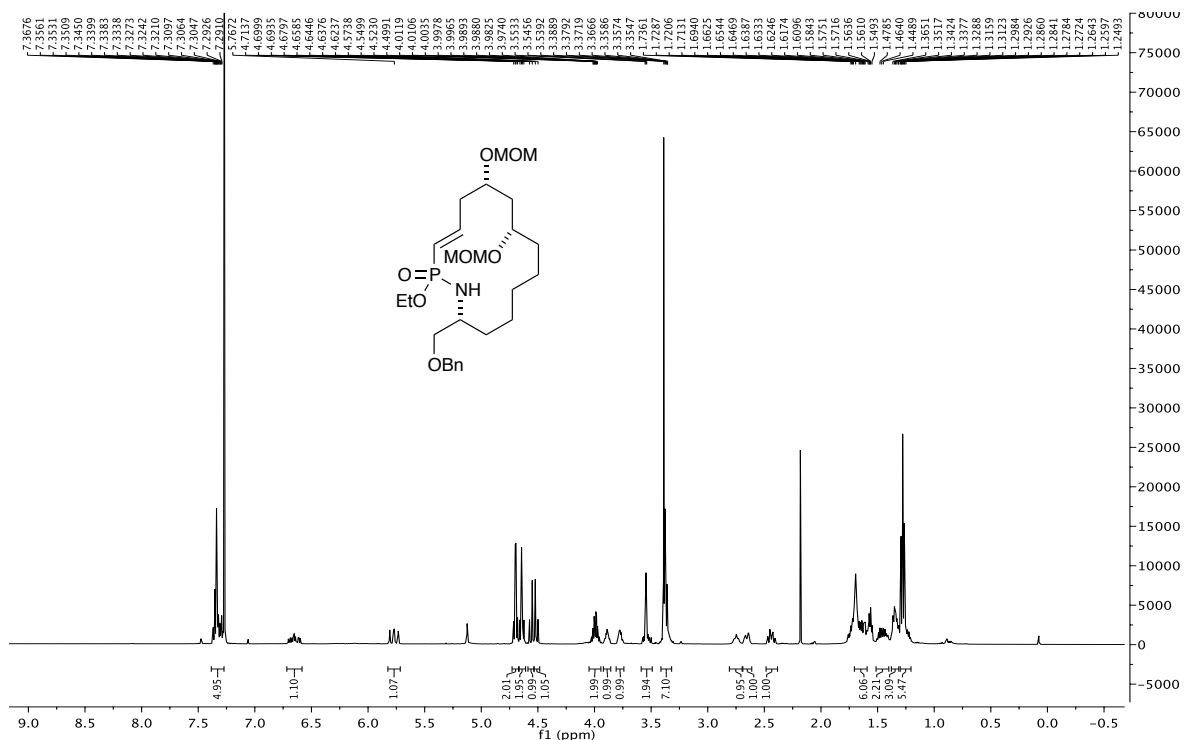


[illegible]

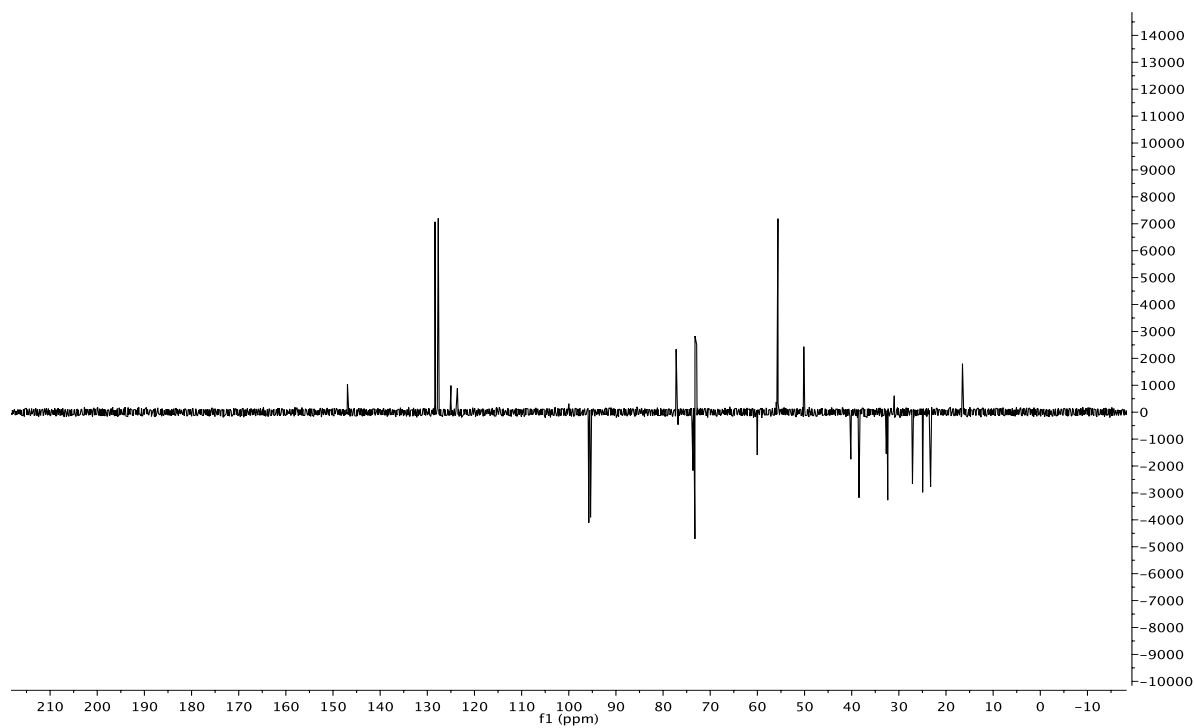
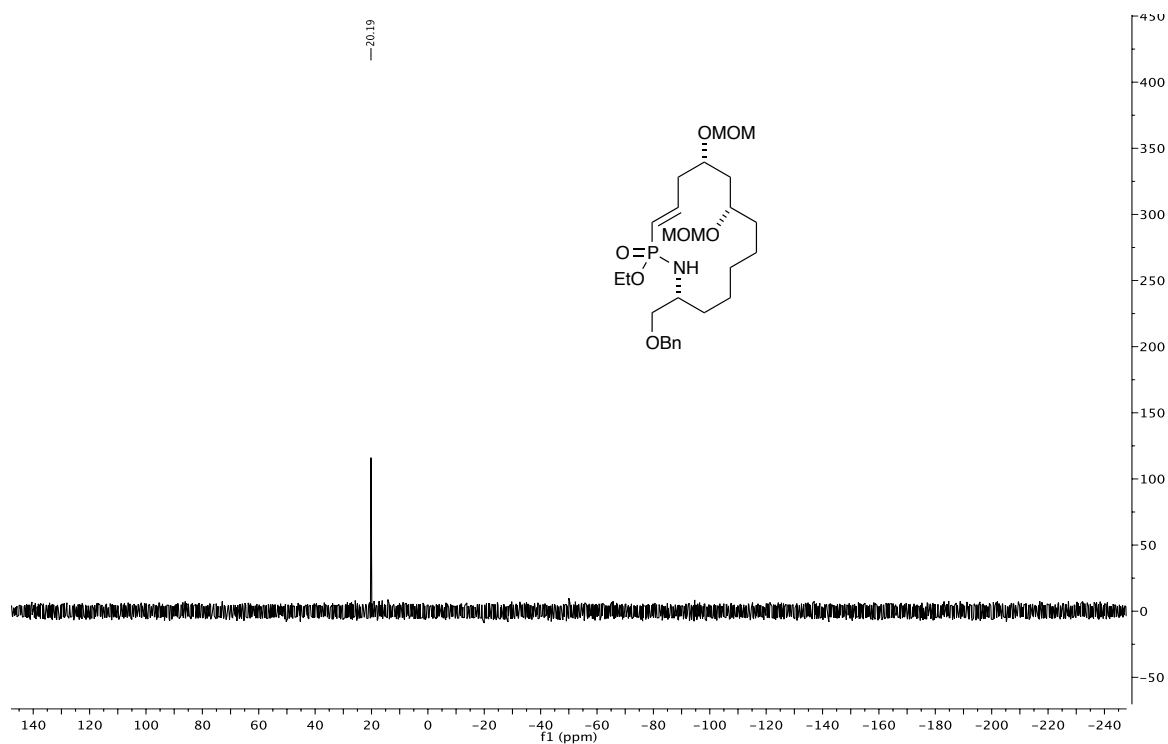
ene 1,1-dioxide (**2.3c**):

Chemical structure of **2.3e** is shown above the spectrum.

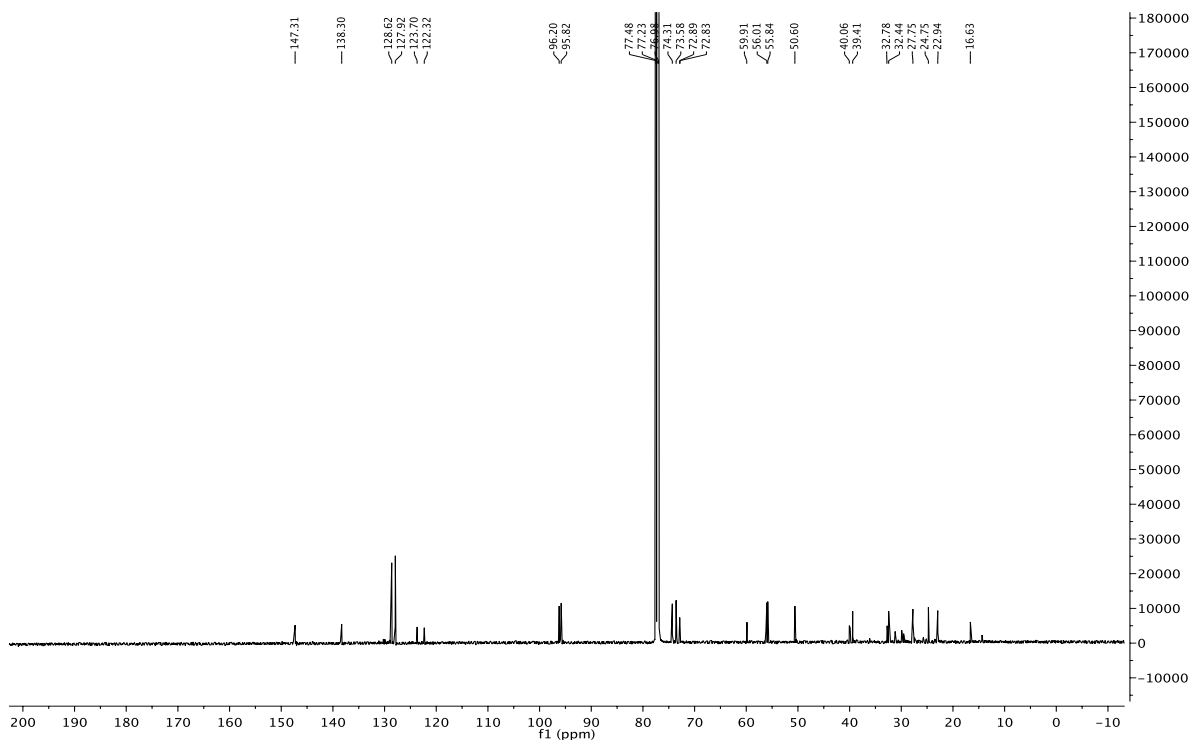
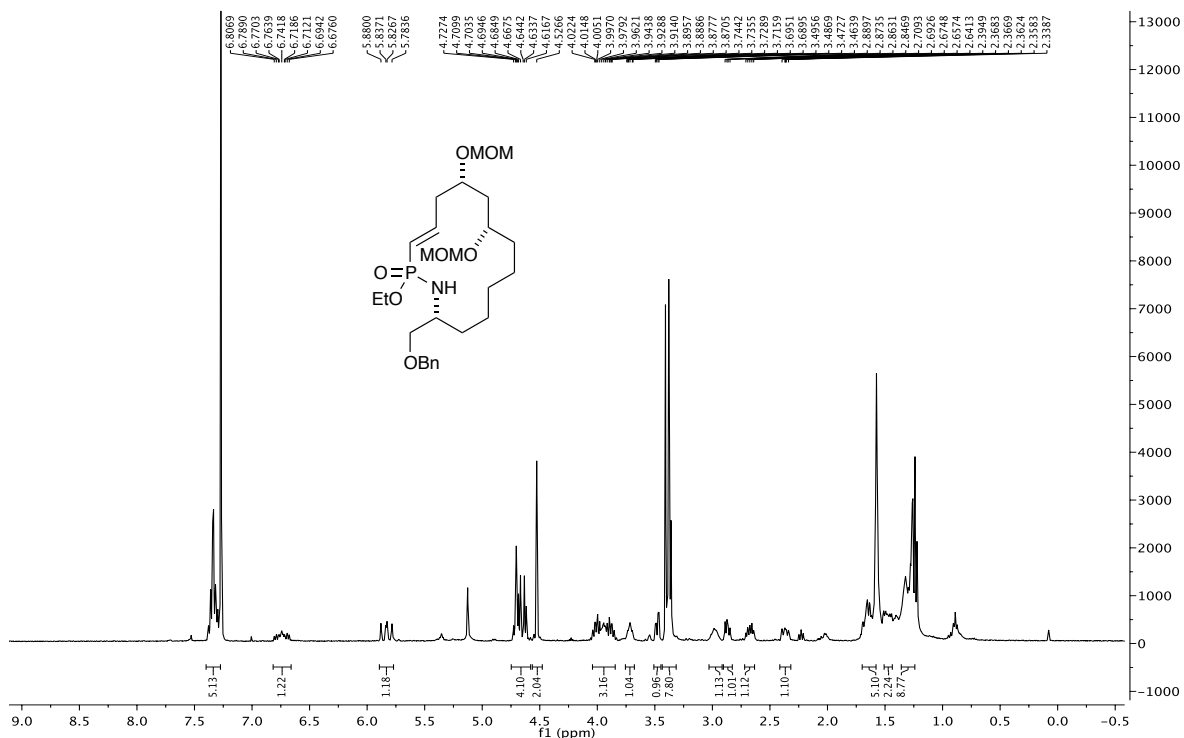
(6*S*,8*S*,14*S*,*E*)-14-((Benzyloxy)methyl)-2-ethoxy-6,8-bis(methoxymethoxy)-1-aza-2-phosphacyclotetradec-3-ene 2-oxide [Diastereomer-1, 2.3f, (*R_P* and *S_P*)]:



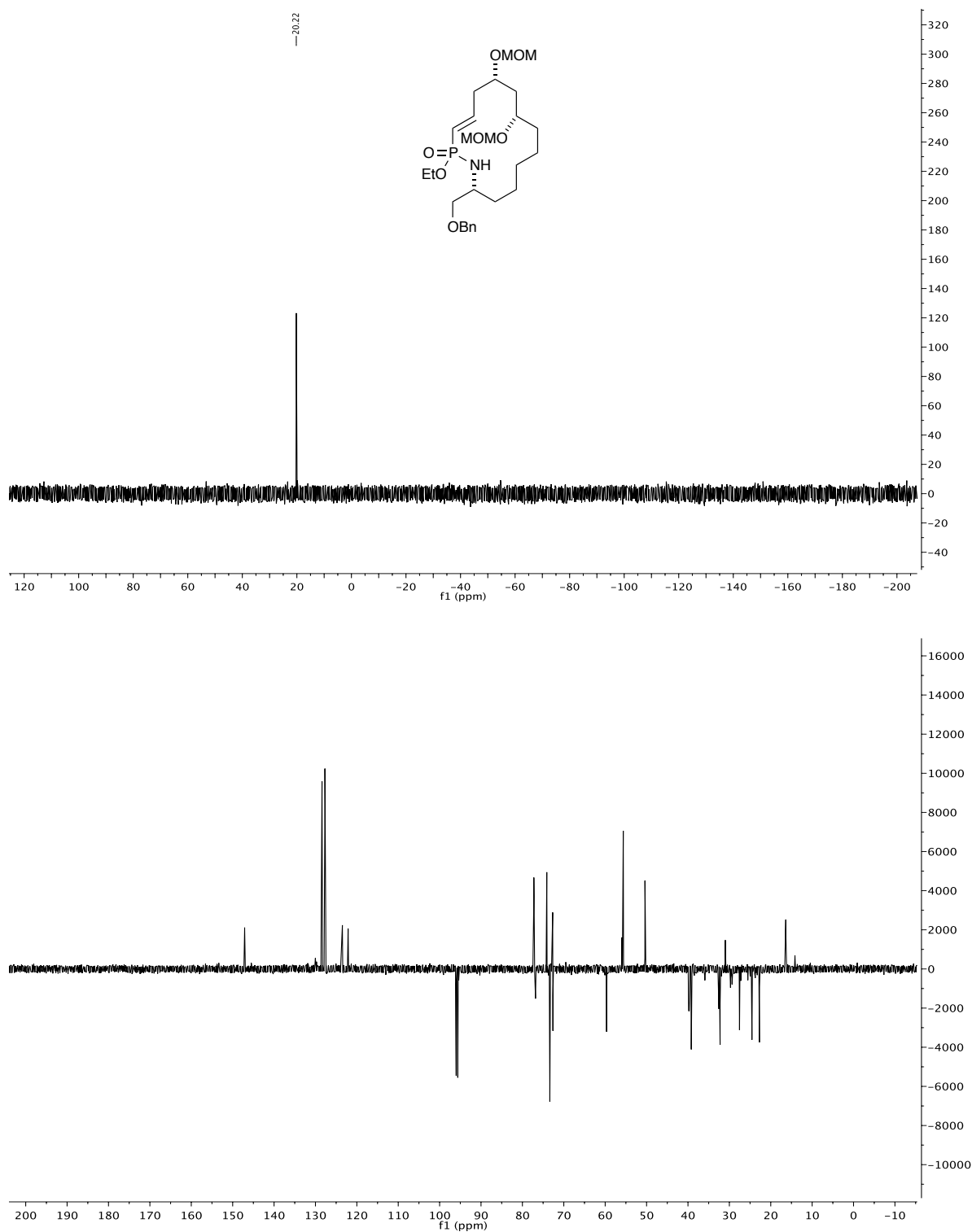
(6*S*,8*S*,14*S*,*E*)-14-((Benzyloxy)methyl)-2-ethoxy-6,8-bis(methoxymethoxy)-1-aza-2-phosphacyclotetradec-3-ene 2-oxide [Diastereomer-1, 2.3f*, (*R_P* and *S_P*)]:



(6*S*,8*S*,14*S*,*E*)-14-((Benzyloxy)methyl)-2-ethoxy-6,8-bis(methoxymethoxy)-1-aza-2-phosphacyclotetradec-3-ene 2-oxide [Diastereomer-2, 2.3f, (*R_P* and *S_P*)]:

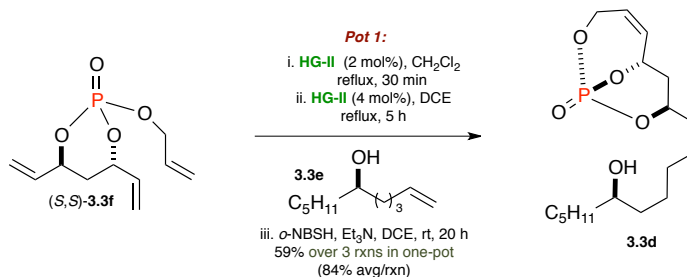


(6*S*,8*S*,14*S*,*E*)-14-((Benzyloxy)methyl)-2-ethoxy-6,8-bis(methoxymethoxy)-1-aza-2-phosphacyclotetradec-3-ene 2-oxide [Diastereomer-2, 2.3f, (*R_P* and *S_P*)]:



5.2a: A Pot-Economical Approach to the Total synthesis of Sch-725674 (Chapter 3)

One-pot RCM, CM, chemoselective hydrogenation sequential protocol to (6*S*,8*R*)-8-((*R*)-6-hydroxyundecyl)-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-ene-1-oxide (**3.3d**):



To a stirred solution of (*S,S*)-triene **3.3f**⁴ (2.0 g, 8.69 mmol) in a freshly distilled, freeze-degas-thawed CH₂Cl₂ (1.08 L, 0.008 M) was added Hoveyda-Grubbs 2nd Gen. catalyst (**HG-II**) (108 mg, 0.17 mmol, 2 mmol%) and the reaction was heated to reflux for 30 min. After completion of RCM, CH₂Cl₂ was completely removed under reduced pressure. Next, freshly distilled, freeze-degas-thawed 1,2-dichloroethane (DCE) (174 mL, 0.05 M) was added to the crude RCM product. The cross partner **3.3e**⁵ (1.77 g, 10.4 mmol) and **HG-II** (216 mg, 0.34 mmol, 4 mmol%) were introduced under argon atmosphere. The reaction was refluxed for an additional 5 h until completion of the CM reaction (monitored by TLC). The reflux was stopped, and *o*-nitrobenzenesulfonyl hydrazine (*o*-NBSH) (18.86 g, 86.9 mmol) and Et₃N (37.7 mL, at 2 mL/g of *o*-NBSH) were added at room temperature and the reaction was stirred for about 12 h. Next, excess *o*-NBSH (9.43 g, 43.45 mmol) and Et₃N (18.8 mL, at 2 mL/g of *o*-NBSH) were added. The reaction was stirred for an additional 8 h at the same temperature until the crude

[4]. For the preparation of (*S,S*)-**8**, see: (a) Whitehead, A.; McReynolds, M. D.; Moore, J. D.; Hanson, P. R. *Org. Lett.* **2005**, 7, 3375–3378. (b) Thomas, C. D.; McParland, J. M.; Hanson, P. R. *Eur. J. Org. Chem.* **2009**, 5487–5500. (c) Venukadasula, P. K. M.; Chegondi, R.; Maitra, S.; Hanson, P. R. *Org. Lett.* **2010**, 12, 1556–1559.

[5]. For the preparation of **9**, see: Kubizna, P.; Špánik, I.; Kožíšek, J.; Szolcsányi, P. *Tetrahedron* **2010**, 66, 2351–2355.

NMR showed the absence of starting material (CM product). A saturated solution of NaHCO₃ (50 mL) was added to the reaction mixture and diluted with excess EtOAc (400 mL). The organic layer was separated and aqueous phase was extracted with EtOAc (2x100 mL). The combined organic layers were washed with brine (80 mL), dried (Na₂SO₄), concentrated under reduced pressure, and subjected to flash chromatography (25% EtOAc/CH₂Cl₂) to provide phosphate **3.3d** as a brownish semi solid (1.77 g, 59% over 3 rxns in one-pot, 84% avg/rxn).

Optical Rotation: $[\alpha]_D^{23} +58.0$ (*c* 0.25, CHCl₃);

FTIR (neat): 3405, 2929, 2856, 1463, 1292, 1101, 1070, 975, 877 cm⁻¹;

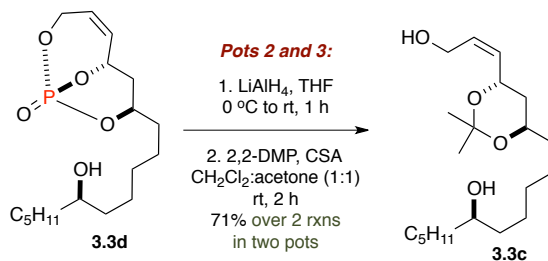
¹H NMR (400 MHz, Chloroform-*d*): δ 6.07–5.99 [m, 1H, -CH=CHCH₂OP(O)-], 5.59 [dt, *J* = 11.9, 3.5 Hz, 1H, -CH=CHCH₂OP(O)-], 5.18 [d, *J* = 24.0 Hz, 1H, -CH₂CHP(O)CH=CH-], 5.00 [ddd, *J* = 15.0, 6.1, 3.1 Hz, 1H, -CH₂CH₂CHOP(O)CH₂], 4.61–5.51 [m, 1H, -CH=CHCH_aH_bOP(O)-], 4.36 [ddd, *J* = 27.6, 14.9, 6.7 Hz, 1H, 1H, -CH=CHCH_aH_bOP(O)-], 3.62–3.53 [m, 1H, -CH₂CH(OH)CH₂], 2.17 [ddd, *J* = 18.1, 11.9, 6.0 Hz, 1H, -CHOP(O)CH_aH_bCHOP(O)-], 1.82–1.65 [m, 2H, -CH_aH_bCHOP(O)CH_aH_bCHOP(O)-], 1.64–1.19 [m, 17H, aliphatic protons and -CH_aH_bCHOP(O)CH_aH_bCHOP(O)-], 0.89 [t, *J* = 6.8 Hz, 3H, CH₃];

¹³C NMR (126 MHz, Chloroform-*d*): δ 129.9, 127.9, 76.7, 71.9, 62.94, 62.89, 37.5, 37.2, 35.6, 34.8, 31.9, 29.2, 25.4, 25.3, 24.5, 22.6, 14.0;

³¹P NMR (162 MHz, Chloroform-*d*): δ -3.72;

HRMS: calculated for C₁₇H₃₁NaO₅P (M+Na)⁺ 369.1807; found 369.1825 (TOF MS ES+).

(*R*)-1-((4*R*,6*S*)-6-((*Z*)-3-Hydroxyprop-1-en-1-yl)-2,2-dimethyl-1,3-dioxan-4-yl)undecan-6-ol (3.3c):



To a stirring solution of phosphate **3.3d** (1.5 g, 4.33 mmol) in anhydrous THF (45 mL) was added LiAlH_4 (0.494 g, 13.0 mmol) in portions at 0 °C under argon atmosphere. The reaction was stirred at the same temperature for 1 h. After reaction completion (monitored by TLC), it was quenched with the slow sequential addition of H_2O (1.5 mL), followed by 10% NaOH (1.5 mL) and H_2O (4.5 mL) [Fieser workup].⁶ The mixture was warmed to room temperature and stirred for another 30 min and added 10% HCl (pH ~ 4). The aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (40 mL), dried over Na_2SO_4 and concentrated under reduced pressure to give the crude tetrol (1.35 g) as a white solid. Without chromatographic purification, the crude tetrol was directly subjected to the next step.

To a stirring solution of the above crude tetrol (1.35 g) in a 1:1 mixture of CH_2Cl_2 and acetone (25 mL) was added 2,2-dimethoxy propane (6 mL) and followed by a catalytic amount of CSA (50 mg, 0.216 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 2 h. Next, it was treated with aqueous saturated NaHCO_3 solution (15 mL) and diluted with CH_2Cl_2 (120 mL). The organic layer was separated and the aqueous layer was back extracted with CH_2Cl_2 (2 x 50 mL). The combined organic

[6]. (a) Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*, Vol. 1; Wiley: New York, 1967; pp 581–595. (b) Mićović, V. M.; Mihailović, M. L. The reduction of acid amides with lithium aluminum hydride. *J. Org. Chem.* **1953**, *18*, 1190–1200.

layers were washed with brine (40 mL), dried (Na₂SO₄), filtered and concentrated in *vacuo*. The crude material was purified using silica gel column chromatography (25% EtOAc/Hexanes) to afford 1,3-acetonide **3.3c** (1.05 g, 71% over 2 rxns in 2 pots) as a colorless liquid.

Optical Rotation: $[\alpha]_{\text{D}}^{23} -41.6$ (*c* 0.25, CHCl₃);

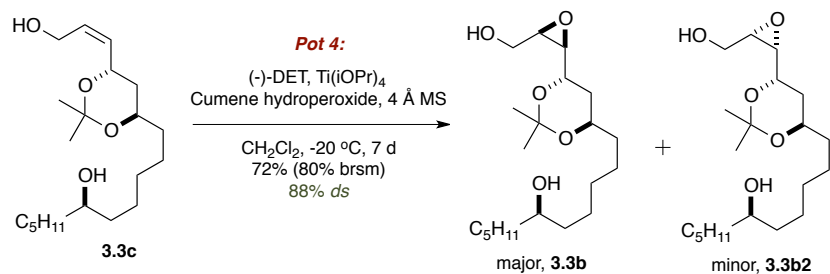
FTIR (neat): 3415, 3384, 2929, 2856, 1629, 1458, 1379, 1222, 1033, 1010 cm⁻¹;

¹H NMR (400 MHz, Chloroform-*d*): δ 5.76 (dt, *J* = 12.4, 6.5 Hz, 1H), 5.58 (dd, *J* = 11.3, 7.1 Hz, 1H), 4.65 (dd, *J* = 15.3, 7.3 Hz, 1H), 4.26 (dd, *J* = 13.3, 6.7 Hz, 1H), 4.15 (dd, *J* = 13.3, 6.6 Hz, 1H), 3.87–3.77 (m, 1H), 3.62–3.53 (m, 1H), 1.98 (bs, 1H), 1.79–1.60 (m, 2H), 1.59–1.49 (m, 1H), 1.49–1.20 (m, 23H), 0.89 (t, *J* = 6.4 Hz, 3H);

¹³C NMR (126 MHz, Chloroform-*d*): δ 132.6, 131.1, 100.4, 71.9, 66.4, 63.5, 58.9, 38.7, 37.4, 37.3, 35.8, 31.9, 29.5, 25.5, 25.3 (2C), 25.3, 24.6, 22.6, 14.0;

HRMS: calculated for C₂₀H₃₈NaO₄ (M+Na)⁺ 365.2668; found 365.2564 (TOF MS ES+).

(*R*)-1-((4*R*,6*S*)-6-((2*S*,3*R*)-3-(hydroxymethyl)oxiran-2-yl)-2,2-dimethyl-1,3-dioxan-4-yl)undecan-6-ol (3.3b**):**



To a stirred suspension of (–)-diethyl tartrate (72 mg, 0.35 mmol) and 4Å MS in anhydrous CH₂Cl₂ (3.0 mL) at -20 °C was added titanium isopropoxide (85 µL, 0.292 mmol) under argon atmosphere. The suspension was stirred for 20 min at the same temperature. Next, cumene hydroperoxide (115 µL, 0.605 mmol, 80%) was added slowly to the reaction mixture and allowed to stir for 20 min. A solution of allyl alcohol **3.3c** (100 mg, 0.292 mmol) in CH₂Cl₂ (1.5 mL) was added dropwise and allowed to stir at -20 °C for 7 days until TLC indicated most of the starting material was consumed (stirring during day, freezer at night). The reaction mixture was quenched with NaOH in aq. saturated Na₂SO₄ solution (100 mg in 1.5 mL) and stirred for 2 h at the room temperature. The quenched mixture was filtered through celite and EtOAc (3x10 mL) was used to wash the filter cake. The filtrate (EtOAc soln) was washed with brine (10 mL), dried (Na₂SO₄) and concentrated under reduced pressure. The crude material was subjected to column chromatography (28-30% EtOAc/Hexanes) to afford a major diastereomer **3.3b** (67 mg, 64%, 88% *ds*) and minor diastereomer **3.3b2** (9.0 mg, 8.6%) as colorless liquids, along with recovered starting material **3.3c** (10.0 mg).

Optical Rotation: [α]_D²³ –8.4 (*c* 0.25, CHCl₃);

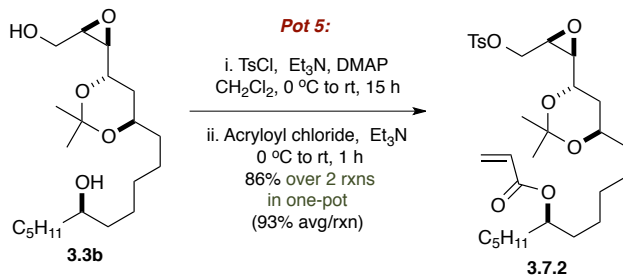
FTIR (neat): 3398, 3379, 2985, 2856, 1456, 1379, 1225, 1027, 895 cm^{–1};

¹H NMR (400 MHz, Chloroform-*d*): δ 3.91–3.82 (m, 2H), 3.77 (dd, J = 14.6, 7.4 Hz, 1H), 3.69 (dd, J = 12.2, 6.3 Hz, 1H), 3.63–3.54 (m, 1H), 3.35 (s, 1H), 3.25 (dd, J = 10.7, 5.8 Hz, 1H), 3.04 (dd, J = 7.3, 4.3 Hz, 1H), 1.95 (ddd, J = 14.3, 8.5, 6.2 Hz, 1H), 1.83 (ddd, J = 15.1, 8.2, 6.3 Hz, 1H), 1.63–1.18 (m, 24H), 0.90 (t, J = 6.6 Hz, 3H);

¹³C NMR (126 MHz, Chloroform-*d*): δ 100.4, 71.9, 66.3, 66.1, 61.1, 58.3, 55.9, 37.4, 37.3, 36.2, 35.8, 31.9, 29.5, 25.5, 25.54, 25.3, 25.2, 24.7, 22.6, 14.0;

HRMS: calculated for C₂₀H₃₈NaO₅ (M+Na)⁺ 381.2617; found 381.2074 (TOF MS ES+).

One-pot tosylation, acryloylation sequential protocol to **(*R*)-1-((4*R*,6*S*)-2,2-dimethyl-6-((2*S*,3*R*)-3-((tosyloxy)methyl)oxiran-2-yl)-1,3-dioxan-4-yl)undecan-6-yl acrylate (3.7.2)**:



To a stirred solution of epoxy diol **3.3b** (500 mg, 1.39 mmol) in CH₂Cl₂ (25 mL) was added Et₃N (0.4 mL, 2.78 mmol), followed by the addition of DMAP (34 mg, 0.278 mmol) at 0 °C under argon atmosphere. After being stirred for 15 min at the same temperature, it was treated with toluene-*p*-sulfonyl chloride (0.53 g, 2.78 mmol). The reaction mixture was stirred at room temperature for 15 h. Upon consumption of starting material (monitored by TLC), the mixture was cooled to 0 °C and more Et₃N (1.0 mL, 6.95 mmol) was added, followed by the slow addition of acryloyl chloride (282 μ L, 3.47 mmol). The resulting mixture was stirred at room temperature for 1 h (reaction progress was monitored by TLC, and was subsequently quenched with saturated NH₄Cl solution

(10 mL). The organic layer was separated and aqueous phase was extracted with CH₂Cl₂ (2 x 15 mL). The combined organic layers were washed with brine (10 mL), then dried (Na₂SO₄), filtered and concentrated in *vacuo*. The resulting crude oil was chromatographed over silica gel (12% EtOAc/Hexanes) to afford the desired product **3.7.2** (0.68 g, 86% over 2 rxns in one-pot, 93% avg/rxn) as a pale yellow gummy liquid.

Optical Rotation: $[\alpha]_D^{23} +8.8$ (*c* 0.25, CHCl₃);

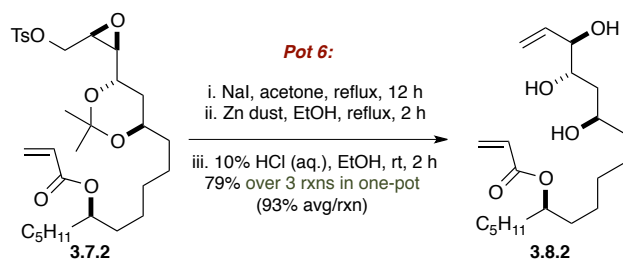
FTIR (neat): 2931, 2858, 1720, 1579, 1460, 1369, 1190, 979, 812 cm⁻¹;

¹H NMR (500 MHz, Chloroform-*d*): δ 7.81 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 8.3 Hz, 2H), 6.39 (dd, *J* = 17.2, 1.5 Hz, 1H), 6.11 (dd, *J* = 17.2, 10.3 Hz, 1H), 5.81 (dd, *J* = 10.4, 1.5 Hz, 1H), 4.95 (tt, *J* = 7.1, 5.3 Hz, 1H), 4.42 (dd, *J* = 11.6, 3.1 Hz, 1H), 4.05 (dd, *J* = 11.6, 7.4 Hz, 1H), 3.80–3.74 (m, 1H), 3.63 (dt, *J* = 8.8, 6.4 Hz, 1H), 3.23 (ddd, *J* = 7.4, 4.2, 3.2 Hz, 1H), 3.02 (dd, *J* = 6.7, 4.3 Hz, 1H), 2.46 (s, 3H), 1.84 (ddd, *J* = 14.7, 8.9, 5.8 Hz, 1H), 1.69 (ddd, *J* = 15.4, 9.3, 6.2 Hz, 1H), 1.60–1.45 (m, 8H), 1.44–1.19 (m, 16H), 0.87 (t, *J* = 6.5, 3H);

¹³C NMR (126 MHz, Chloroform-*d*): δ 166.1, 145.1, 132.7, 130.2, 129.9 (2), 128.9, 128.0 (2), 100.3, 74.5, 68.5, 66.2, 65.0, 57.9, 53.7, 36.0, 35.7, 34.1, 31.7, 29.7, 29.4, 25.2, 25.1 (2C), 24.9, 24.4, 22.5, 21.7, 14.0;

HRMS: calculated for C₃₀H₄₆NaO₈S (M+Na)⁺ 589.2811; found 589.2831 (TOF MS ES+).

One-pot Finkelstein substitution, Boord olefination, acetonide deprotection sequential protocol to **(6*R*,12*R*,14*S*,15*R*)-12,14,15-Trihydroxyheptadec-16-en-6-yl acrylate (3.8.2)**:



To a stirring solution of tosylate **3.7.2** (100 mg, 0.176 mmol) in acetone (3 mL) was added sodium iodide (526 mg, 3.52 mmol) and the reaction mixture was heated to reflux for 12 h. After consumption of the starting material (indicated by TLC), acetone was removed under reduced pressure, and EtOH (5 mL) was added to the resulting mixture at room temperature, followed by the addition of activated Zn powder (344 mg, 5.33 mmol). The reaction was heated to reflux for 2 h until TLC indicated the absence of the iodo-derivative. The reaction mixture was cooled to room temperature and subsequently treated with slow addition of 10% aq. HCl (2.0 mL). Stirring was continued for 2 h and the mixture was quenched with saturated aq. NaHCO₃ solution (8.0 mL, until pH = 5). EtOH was completely removed under *vacuo* and to the resulting residue was added EtOAc (20 mL), followed by and H₂O (5 mL). The organic layer was removed and aqueous layer was again extracted with EtOAc (2x10 mL). The combined organic layers were washed with brine (10 mL), dried (Na₂SO₄), filtered and concentrated under *vacuo*. The crude material was subjected to silica gel column chromatography (50%

EtOAc/Hexanes) to provide triol **3.8.2** (49 mg, 79% over 3 rxns in one-pot, 93% avg/rxn) as a colorless gummy oil. Compound **3.8.2** matched the reported material in all respects.⁷

Optical Rotation: $[\alpha]_{\text{D}}^{23} -2.91$ (c 0.3, CHCl_3);

FTIR (neat): 3398, 3361, 2939, 1720, 1404, 1271, 1195, 1045, 983, 808 cm^{-1} ;

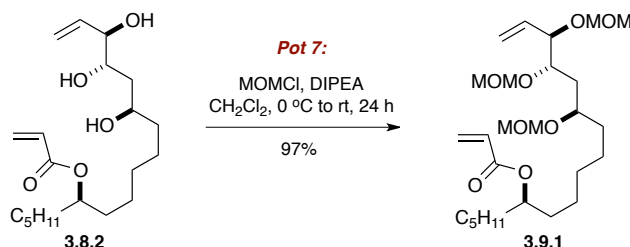
^1H NMR (400 MHz, Chloroform- d): δ 6.38 (dd, $J = 17.3, 1.2$ Hz, 1H), 6.11 (dd, $J = 17.2, 10.4$ Hz, 1H), 5.91 (ddd, $J = 17.2, 10.4, 6.1$ Hz, 1H), 5.81 (d, $J = 10.4$ Hz, 1H), 5.35 (d, $J = 17.2$ Hz, 1H), 5.27 (d, $J = 10.5$ Hz, 1H), 4.95 (p, $J = 6.4$ Hz, 1H), 4.14 (t, $J = 5.4$ Hz, 1H), 4.02–3.90 (m, 2H), 2.72 (s, 1H), 2.26–2.02 (m, 2H), 1.70 (ddd, $J = 14.3, 9.5, 2.8$ Hz, 1H), 1.56–1.49 (m, 6H), 1.48–1.41 (m, 1H), 1.38–1.21 (m, 12H), 0.88 (t, $J = 6.8$ Hz, 3H);

^{13}C NMR (126 MHz, Chloroform- d): δ 166.2, 136.4, 130.4, 128.9, 117.6, 76.1, 74.5, 71.2, 69.3, 37.4, 37.2, 34.1, 34.0, 31.7, 29.2, 25.6, 25.1, 24.9, 22.5, 14.0;

HRMS: calculated for $\text{C}_{20}\text{H}_{36}\text{NaO}_5$ ($\text{M}+\text{Na}$)⁺ 379.2460; found 379.2400 (TOF MS ES+).

[7]. Bali, A. K.; Sunnam, S. K.; Prasad, K. R. *Org. Lett.* **2014**, *16*, 4001–4008.

(6*R*,12*R*,14*S*,15*R*)-12,14,15-tris(Methoxymethoxy)heptadec-16-en-6-yl acrylate (3.9.1):



To a stirring solution of triol **3.8.2** (30 mg, 0.084 mmol) in anhydrous CH₂Cl₂ (1.5 mL) under argon atmosphere was added *N,N*-disopropylethylamine (110 µL, 0.63 mmol). After being stirred for 15 min, chloro(methoxy)methane (34 µL, 0.42 mmol) was added slowly at 0 °C. The reaction mixture was stirred at room temperature for 15 h; then excess *N,N*-disopropylethylamine (110 µL, 0.63 mmol) and chloro(methoxy)methane (34 µL, 0.42 mmol) were added at 0 °C. The stirring was continued for another 9 h at room temperature (until TLC showed the absence of starting material). Upon reaction completion, saturated NaHCO₃ (5.0 mL) was added followed by CH₂Cl₂ (15 mL). The organic layer was separated and the aqueous layer was back extracted with CH₂Cl₂ (2x5 mL). The combined CH₂Cl₂ extracts were washed with brine (5.0 mL), dried (Na₂SO₄), filtered and concentrated under reduced pressure. The obtained crude material was subjected to silica gel column chromatography (15% EtOAc/Hexanes) to furnish the tri-MOM protected diene **3.9.1** (40 mg, 97%) as a colorless liquid.

Optical Rotation: $[\alpha]_D^{23} -30.1$ (*c* 0.25, CHCl₃);

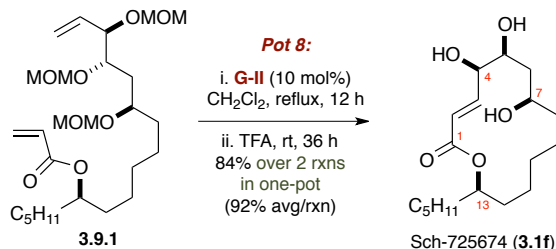
FTIR (neat): 3033, 2821, 1720, 1465, 1404, 1296, 1271, 1195, 1149, 1099, 1035, 918 cm⁻¹;

^1H NMR (400 MHz, Chloroform-*d*): δ 6.38 (d, J = 17.2, 1H), 6.11 (dd, J = 17.2, 10.4 Hz, 1H), 5.84–5.71 (m, 2H), 5.33–5.25 (m, 2H), 4.94 (p, J = 6.2 Hz, 1H), 4.83 (d, J = 6.8 Hz, 1H), 4.73–4.65 (m, 4H), 4.62 (d, J = 6.7 Hz, 1H), 4.16 (d, J = 7.3 Hz, 1H), 3.87–3.81 (m, 1H), 3.73–3.65 (m, 1H), 3.42 (s, 3H), 3.38 (s, 6H), 1.65–1.46 (m, 8H), 1.38–1.16 (m, 12H), 0.88 (t, J = 6.8 Hz, 3H);

^{13}C NMR (126 MHz, Chloroform-*d*): δ 166.1, 134.5, 130.2, 129.0, 119.0, 96.9, 96.1, 94.1, 79.6, 77.1, 75.3, 74.5, 55.9, 55.6, 55.4, 36.3, 35.3, 34.1 (2C), 31.7, 29.8, 25.3, 24.9, 24.8, 22.5, 14.0;

HRMS: calculated for $\text{C}_{26}\text{H}_{48}\text{NaO}_8$ ($\text{M}+\text{Na}$) $^+$ 511.3247; found 511.3239 (TOF MS ES+).

One-pot RCM, MOM deprotection sequential protocol to **(5*R*,6*S*,8*R*,14*R*,*E*)-5,6,8-Trihydroxy-14-pentyloxacyclotetradec-3-en-2-one (3.1f)**:



To a stirred solution of tri-MOM protected diene **3.9.1** (10 mg, 0.02 mmol) in a freshly distilled, freeze-degas-thawed CH_2Cl_2 (14 mL, 0.0015 M) was added the Grubbs 2nd generation catalyst (**G-II**) (1.0 mg, 6 mol%). The reaction was heated to reflux for 6 h and cooled down to room temperature to add a second batch of **G-II** (0.7 mg, 4 mol%). The reflux was resumed for 6 h (until the RCM completed by TLC). The solvent was reduced to a final volume of approximately 1.0 mL by removing the reflux condenser from the reaction flask. The reaction mixture was then cooled to room temperature and treated with TFA (1.5 mL) under argon atmosphere. The reaction was allowed to stir for

36 h (reaction progress was monitored by TLC) and the volatiles were removed under *vacuo*. The crude residue was chromatographed over silica gel (75% EtOAc/Hexanes) to furnish the target natural product, Sch-725674 (**3.1f**) (5.6 mg, 84% over 2 rxns in one-pot, 92% avg/rxn) as a colorless solid. Characterization data noted below was compared and matched to those reported by Prasad⁷ and Curran.⁸

M.P. Range: 181–183 °C;

Optical Rotation: $[\alpha]_{\text{D}}^{23} +4.97$ (c 0.15, CH₃OH), {Reported: $[\alpha]_{\text{D}} +5.15$ (c 0.27, CH₃OH)};

FTIR (neat): 3451, 2931, 1708, 1279, 1068, 983, 896, 805 cm⁻¹;

¹H NMR (400 MHz, Methanol-*d*₄): δ 6.87 [dd, J = 15.8, 6.1 Hz, 1H, -CH=CH(C=O)O-], 6.08 [dd, J = 15.8, 1.5 Hz, 1H, -CH=CH(C=O)O-], 4.98–4.93 [m, 1H, CH₂CH(OC=O)CH₂CH₃], 4.51–4.46 [m, 1H, -CH=CHCH(OH)-], 3.99 [p, J = 6.1 Hz, 1H, -CH₂CH(OH)CH₂-], 3.85 [dd, J = 6.3, 4.4 Hz, 1H, -CH₂CH(OH)CH(OH)-], 1.83 [dt, J = 14.7, 6.0 Hz, 1H, -CH(OH)CH_aH_bCH(OH)-], 1.73–1.51 (m, 5H, aliphatic protons), 1.40–1.25 (m, 11H, aliphatic protons), 1.23–1.12 (m, 3H, aliphatic protons), 0.90 (t, J = 6.8 Hz, 3H, CH₃);

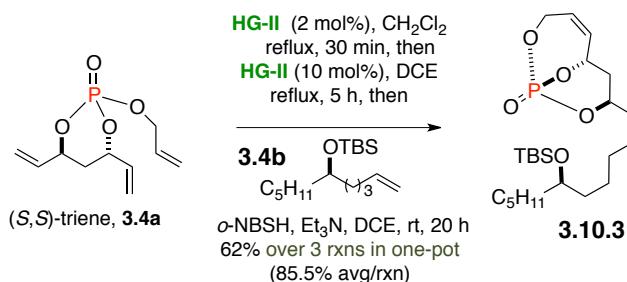
¹³C NMR (126 MHz, Methanol-*d*₄): δ 168.4, 149.3, 123.1, 77.6, 76.0, 72.9, 69.5, 38.3, 36.8, 36.5, 34.1, 32.9, 29.5, 27.0, 26.4, 25.8, 23.8, 14.5;

HRMS: calculated for C₁₈H₃₂NaO₅ (M+Na)⁺ 351.2147; found 351.2135 (TOF MS ES+).

[8]. Moretti, J. D.; Wang, X.; Curran, D. P. *J. Am. Chem. Soc.* **2012**, *134*, 7963–7970.

5.2b: A pot-economical approach for the total syntheses of Sch-725674 analogs (Chapter-3).

(1*S*,6*S*,8*R*)-8-((*R*)-6-((*tert*-butyldimethylsilyl)oxy)undecyl)-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-ene 1-oxide (3.10.3):



To a solution of (*S,S*)-triene **3.4a**⁹ (500 mg, 2.17 mmol) in a degassed CH₂Cl₂ (434 mL, 0.005 M) was added **HG-II** (40 mg, 0.065 mmol, 3 mol%) and the reaction mixture was refluxed for 30 min. After completion of RCM, CH₂Cl₂ was evaporated under reduced pressure. To the crude product was added freshly distilled, freeze-degas-thawed 1,2-dichloroethane (DCE) (43 mL, 0.05 M), the cross metathesis (CM) partner **3.4b**¹⁰ (1.77 g, 2.8 mmol) and **HG-II** (130 mg, 0.13 mmol, 6 mol%) under argon. The reaction mixture was heated at 70 °C for 5 h and a second portion of **HG-II** (54 mg, 0.086 mmol, 4 mol%) and CM partner **3.4b** (408 mg, 0.65 mmol) were added to the reaction mixture. The reaction mixture was stirred at 70 °C for an additional 3 h (monitored by TLC). After completion of reaction, it was cooled to room temperature and was added *o*-nitrobenzenesulfonyl hydrazine (*o*-NBSH) (4.70 g, 21.7 mmol) and Et₃N (9.7 mL, at 2 mL/g of *o*-NBSH). The reaction mixture was stirred for 12 h at room temperature. A

[9]. For the preparation of (*S,S*)-**8**, see: (a) Whitehead, A.; McReynolds, M. D.; Moore, J. D.; Hanson, P. R. *Org. Lett.* **2005**, 7, 3375–3378. (b) Thomas, C. D.; McParland, J. M.; Hanson, P. R. *Eur. J. Org. Chem.* **2009**, 5487–5500. (c) Venukadasula, P. K. M.; Chegondi, R.; Maitra, S.; Hanson, P. R. *Org. Lett.* **2010**, 12, 1556–1559.

[10]. For the preparation of **9**, see: Kubizna, P.; Špánik, I.; Kožíšek, J.; Szolcsányi, P. *Tetrahedron* **2010**, 66, 2351–2355.

second portion of *o*-NBSH (2.3 g, 10.85 mmol) and Et₃N (4.6 mL, at 2 mL/g of *o*-NBSH) were added and the reaction mixture was stirred for an additional 8 h. The progress of reaction was monitored by crude NMR, which confirmed the completion of reaction. The reaction mixture was diluted with EtOAc (200 mL) followed by addition of saturated aqueous solution of NaHCO₃ (50 mL). The organic layer was separated and aqueous phase was extracted with EtOAc (3x50 mL). The combined organic layers were washed with brine (40 mL), dried (Na₂SO₄), concentrated under reduced pressure, and purified by flash chromatography (25% EtOAc/CH₂Cl₂), which furnished bicyclic phosphate **3.10.3** as a brownish semi solid (620 mg, 62% over 3 rxns in one-pot, 85.5% avg/rxn).

Optical Rotation: $[\alpha]_D^{23} +57.6$ (*c* 0.5, CHCl₃).

FTIR (neat): 2929, 2856, 1461, 1359, 1303, 1253, 1103, 1070, 973, 835, 773 cm⁻¹.

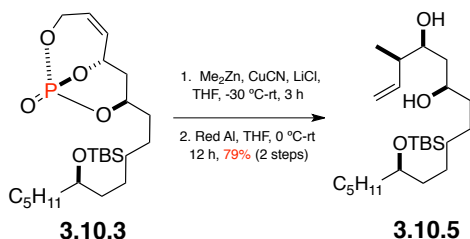
¹H NMR (400 MHz, Chloroform-*d*): δ 6.03 (dddd, *J* = 12.0, 8.9, 5.4, 2.2 Hz, 1H), 5.59 (ddd, *J* = 11.8, 4.0, 2.5 Hz, 1H), 5.24–5.14 (m, 1H), 5.00 (ddt, *J* = 14.7, 5.8, 2.3 Hz, 1H), 4.64 – 4.47 (m, 1H), 4.37 (ddd, *J*_{HP} = 27.7, *J*_{HH} = 14.7, 6.7 Hz, 1H), 3.61 (p, *J* = 5.7 Hz, 1H), 2.17 (ddd, *J* = 16.4, 12.0, 6.3 Hz, 1H), 1.79 – 1.63 (m, 2H), 1.61 – 1.45 (m, 2H), 1.42 – 1.19 (m, 15H), 0.92–0.84 (m, 12H), 0.04 (s, 3H), 0.03 (s, 3H).

¹³C NMR (126 MHz, CDCl₃): δ 130.1, 128.1, 77.4, 76.9, 72.5, 63.1 (d, *J*_{CP} = 6.5 Hz), 37.4, 37.1, 35.9 (d, *J*_{CP} = 9.5 Hz), 35.1 (d, *J*_{CP} = 6.4 Hz), 32.3, 29.7, 26.1 [3xC, Si-C(CH₃)₃], 25.4, 25.2, 24.8, 22.9, 18.4, 14.3, -4.2 [2xC, Si(CH₃)₂].

³¹P NMR (162 MHz, Chloroform-*d*): δ -3.63.

HRMS: calculated for C₂₃H₄₅NaO₅PSi (M+Na)⁺ 483.2672; found 483.2677 (TOF MS ES+).

(3*R*,4*S*,6*R*,12*R*)-12-((*tert*-butyldimethylsilyl)oxy)-3-methylheptadec-1-ene-4,6-diol (3.10.5):



To a flame dried flask containing CuCN (478 mg, 5.3 mmol) and LiCl (529 mg, 12.46 mmol), weighted inside the glove box, was added dry THF (35.6 mL, 0.05 M) under argon and stirred at room temperature for 15 minutes. A pale green coloration was observed. The reaction was cooled to $-30\text{ }^\circ\text{C}$ followed by slow addition of a 1 M solution of Me_2Zn in THF (5.3 mL, 5.3 mmol). The reaction was stirred for 40 minutes at $-30\text{ }^\circ\text{C}$ and a solution of bicyclic phosphate **3.10.3** (820 mg, 1.78 mmol) in dry THF (35.6 mL, 0.05 M) was added drop wise via cannula to the reaction mixture. The reaction was slowly warmed to room temperature and allowed to stir for 3 h. Upon completion of reaction, it was quenched with aqueous ammonium chloride (NH_4Cl). The reaction was stirred for 30 minutes and was added anhydrous Na_2SO_4 (200 mg) stirred for another 20 min. The reaction mixture was filtered through a Celite® pad to get rid of salt particles. The Celite® layer was washed with excess of EtOAc (3x50 mL) and concentrated under reduced pressure, which afforded the crude acid as yellowish colored clear oil, which was proceeded to the next reaction without further purification.

To a flask containing the crude acid was added THF (22 mL, 0.08 M). The reaction mixture was cooled to $0\text{ }^\circ\text{C}$ followed by the addition of a 70% solution of Red-Al in toluene (5.4 mL, 6 mmol). The reaction was brought to room temperature and stirred for 12 hours. After completion of reaction (monitored by TLC) the reaction was

quenched with NH₄Cl (sat'd aq) and extracted with EtOAc (3x100 mL). The organic layer was dried (Na₂SO₄) and the solvent was evaporated under reduced pressure. The crude product was purified via flash chromatography, which afforded TBS-protected diol **3.10.5** (590 mg, with 79% yield over two reactions) as colorless viscous oil.

Optical Rotation: $[\alpha]_D^{23} -0.54$ (*c* 0.37, CHCl₃);

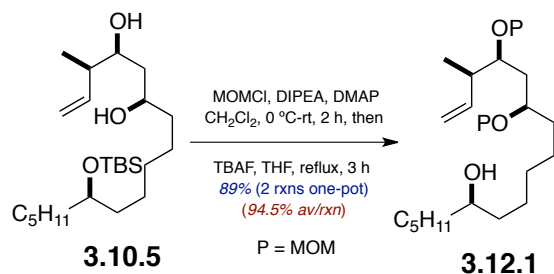
FTIR (neat): 3355, 2929, 2856, 1461, 1253, 1081, 1053, 1004, 912, 835, 773 cm⁻¹;

¹H NMR (500 MHz, Chloroform-*d*): δ 5.79 – 5.70 (m, 1H), 5.18 – 5.13 (m, 2H), 4.00 – 3.87 (m, 1H), 3.75 – 3.68 (m, 1H), 3.62 (p, *J* = 5.7 Hz, 1H), 2.48 (t, *J* = 4.1 Hz, 1H), 2.34 – 2.19 (m, 2H), 1.64 (t, *J* = 6.3 Hz, 2H), 1.60–1.51 (m, 1H), 1.56 – 1.28 (m, 18H), 1.03 (d, *J* = 6.8 Hz, 3H), 0.89 (s, 12H), 0.04 (s, 6H).

¹³C NMR (126 MHz, CDCl₃): δ 140.7, 117.0, 72.5, 72.2, 69.4, 44.7, 39.4, 37.6, 37.3, 37.3, 32.3, 30.1, 26.3 [3xC, Si-C(CH₃)₃], 26.2, 25.5, 25.2, 22.9, 18.4, 16.4, 14.3, -4.2 [2xC, Si(CH₃)₂].

HRMS: calculated for C₂₄H₅₀NaO₃Si (M+Na)⁺ 437.3427; found 437.3442 (TOF MS ES+).

(6*R*,12*R*,14*S*,15*R*)-12,14-bis(methoxymethoxy)-15-methylheptadec-16-en-6-ol (3.12.1):



To a stirred solution of TBS-protected diol **3.10.5**, (200 mg, 0.48 mmol) in CH_2Cl_2 (4.9 mL, 0.1 M) was added DIPEA (496 μL , 2.88 mmol), and DMAP (6.08 mg, 0.04 mmol) followed by drop wise addition of Chloromethyl methyl ether (MOMCl) (108 mL, 1.44 mmol) at 0 $^\circ\text{C}$ under argon. The reaction mixture was stirred at room temperature for 2 h. After completion of reaction (monitored by TLC), the solvent was evaporated under reduced pressure and was added dry THF (4.8 mL, 0.1 M). To the crude reaction mixture was added Tetrabutylammonium fluoride (TBAF, 1 M solution) (1.5 mL, 1.43 mmol) and refluxed for 3 h. After completion of reaction (monitored by TLC), it was quenched with aqueous ammonium chloride (NH_4Cl), extracted with EtOAc (3x40 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude compound was purified by silica gel chromatography (Hexane/EtOAc 3:1), which furnished the MOM-protected alcohol **3.12.1** (176 mg, 89% yield over two reactions, 94.5% av/rxn) as a colorless viscous liquid.

Optical Rotation: $[\alpha]_{\text{D}}^{23} -17.6$ (c 0.5, CHCl_3).

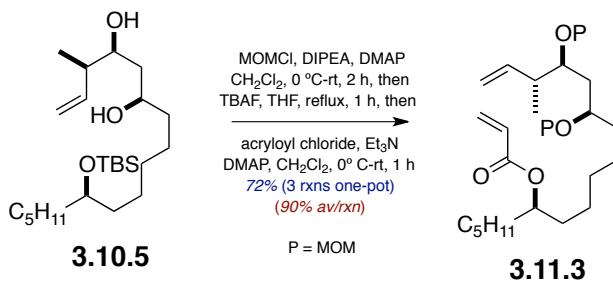
FTIR (neat): 3479, 2929, 2856, 1458, 1375, 1215, 1147, 1099, 1043, 999, 919. cm^{-1} .

¹H NMR (500 MHz, Chloroform-*d*): δ 5.83 – 5.75 (m, 1H), 5.12 – 5.01 (m, 2H), 4.70 (s, 2H), 4.67 (s, 2H), 3.77 – 3.64 (m, 2H), 3.63 – 3.56 (m, 1H), 3.41 (s, 3H), 3.39 (s, 3H), 2.58–2.47(m, 1H), 1.61 – 1.49 (m, 4H), 1.49 – 1.38 (m, 4H), 1.37 – 1.26 (m, 13H), 1.04 (d, J = 6.9 Hz, 3H), 0.90 (t, J = 6.9 Hz, 3H).

¹³C NMR (126 MHz, CDCl₃): δ 140.4, 115.2, 97.0, 96.2, 79.1, 75.7, 72.1, 56.0, 55.9, 41.5, 37.7, 37.6, 36.7, 35.5, 32.1, 30.1, 25.8, 25.6, 25.2, 22.9, 14.3, 14.5.

HRMS: calculated for C₂₂H₄₄NaO₅ (M+Na)⁺ 437.3427; found 437.3442 (TOF MS ES+).

(3*R*,4*S*,6*R*,12*R*)-12-((*tert*-butyldimethylsilyl)oxy)-3-methylheptadec-1-ene-4,6-diol (3.11.3):



To a stirred solution of TBS-protected diol **3.10.5**, (50 mg, 0.12 mmol) in CH₂Cl₂ (0.1 M) was added DIPEA (124 mL, 0.72 mmol), and DMAP (1.52 mg, 0.012 mmol) followed by drop wise addition of Chloromethyl methyl ether (MOMCl) (27 mL, 0.36 mmol) at 0 °C under argon. The reaction mixture was stirred at room temperature for 6 h. After completion of reaction (monitored by TLC), the solvent was evaporated under reduced pressure and was added dry THF (0.1 M). To the crude reaction mixture was added Tetrabutylammonium fluoride (TBAF, 1 M solution) (360 mL 0.36 mmol) and refluxed for 1 h under argon. After completion of reaction (monitored by TLC) the solvent was evaporated and was added CH₂Cl₂ (0.1 M) followed by Et₃N (67 mL, 0.48 mmol) at room temperature. The crude reaction mixture was cooled to 0 °C and was

added acryloyl chloride (29 mL, 0.36 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 1 h. After completion of reaction, it was quenched with ice-cooled water. Extracted with CH₂Cl₂ (3x10 mL), dried (MgSO₄), concentrated and purified using silica gel chromatography (hexane/EtOAc 7:1), which afforded the **3.11.3** (40.7 mg, 72% yield over 3 reactions, 90% av/rxn) as a colorless viscous liquid.

FTIR (neat): 2931, 2860, 1722, 1458, 1404, 1296, 1271, 1195, 1147, 1099, 1035, 916, 810 cm⁻¹.

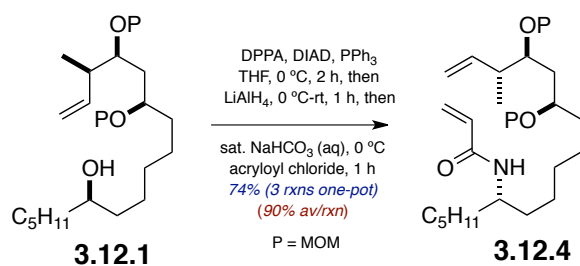
Optical Rotation: $[\alpha]_D^{23} = -9.0$ (*c* 0.5, CHCl₃).

¹H NMR (500 MHz, Chloroform-*d*): δ 6.39 (dd, *J* = 17.3, 1.6 Hz, 1H), 6.12 (dd, *J* = 17.3, 10.4 Hz, 1H), 5.83 – 5.72 (m, 2H), 5.10 – 5.04 (m, 2H), 4.95 (tt, *J* = 7.1, 5.4 Hz, 1H), 4.70 (s, 2H), 4.66 (s, 2H), 3.72 – 3.63 (m, 2H), 3.40 (s, 3H), 3.38 (s, 3H), 1.63 – 1.44 (m, 7H), 1.39 – 1.22 (m, 14H), 1.04 (d, *J* = 6.9 Hz, 3H), 0.89 (t, *J* = 6.5 Hz, 3H).

¹³C NMR (126 MHz, CDCl₃): δ 166.3, 140.5, 130.4, 129.2, 115.2, 97.0, 96.2, 79.1, 75.7, 74.8, 56.0, 55.9, 41.5, 36.7, 35.5, 34.3 (2C), 31.9, 30.0, 25.5, 25.2, 25.1, 22.7, 14.2, 14.0.

HRMS: calculated for C₂₅H₄₆NaO₆ (M+Na)⁺ 465.3192; found 465.3199 (TOF MS ES+).

***N*-((6*S*,12*R*,14*S*,15*R*)-12,14-bis(methoxymethoxy)-15-methylheptadec-16-en-6-yl)acrylamide (**3.12.4**):**



To a solution of MOM-protected alcohol **3.12.1** (70 mg, 0.15 mmol) under argon was added PPh_3 (83 mg, 0.31 mmol) and DIAD (64 mg, 0.31 mmol). The reaction mixture was stirred for 5 min at room temperature and then was added DPPA (90 mg, 0.33 mmol) at $0\text{ }^\circ\text{C}$. The reaction mixture was stirred at the same temperature for 2 h (monitored by TLC). After completion of reaction, LiAlH_4 (12.5 mg, 0.33 mmol) was added in portions at $0\text{ }^\circ\text{C}$ over 5 minutes and the reaction mixture was stirred at the same temperature for 1 h (monitored *via* TLC, the azide was reduced to the corresponding amine). After complete consumption of the starting material the reaction mixture was quenched with aqueous saturated NaHCO_3 solution (1 mL), stirred for 15 min at $0\text{ }^\circ\text{C}$ and diluted with THF (1.2 mL). Acryloyl chloride (29 μL , 0.33 mmol) was added at the same temperature and the reaction mixture was stirred for 1 hour at $0\text{ }^\circ\text{C}$. After completion of acrylation reaction indicated by TLC, the reaction mixture was quenched with NH_4Cl , extracted with EtOAc (3x10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The compound was purified using silica gel chromatography (Hexane/EtOAc 4:1), which afforded the acrylamide **3.12.4** (56 mg, 74% over three reaction one-pot, 90% av/rxn) as colorless viscous liquid.

FTIR (neat): 3272, 2929, 2856, 1654, 1623, 1542, 1147, 1099, 1043, 1916 cm^{-1} .

Optical Rotation: $[\alpha]_{\text{D}}^{23} = -3.2$ (c 0.25, CHCl_3).

^1H NMR (^1H NMR (500 MHz, Chloroform- d): δ 6.28 (dd, $J = 16.9, 1.5$ Hz, 1H), 6.08 (dd, $J = 16.3, 10.3$ Hz, 1H), 5.86 – 5.73 (m, 1H), 5.64 (dd, $J = 10.3, 1.5$ Hz, 1H), 5.22 (d, $J = 9.2$ Hz, 1H), 5.09–5.04 (m, 2H), 4.72 (s, 2H), 4.68 (s, 2H), 4.10 – 3.94 (m, 1H), 3.82 – 3.60 (m, 2H), 3.42 (s, 3H), 3.40 (s, 3H), 2.63 – 2.44 (m, 1H), 1.56 – 1.51 (m, 4H), 1.38 – 1.28 (m, 16H), 1.06 (d, $J = 6.9$ Hz, 3H), 0.9 (t, $J = 7.0$ Hz, 3H).

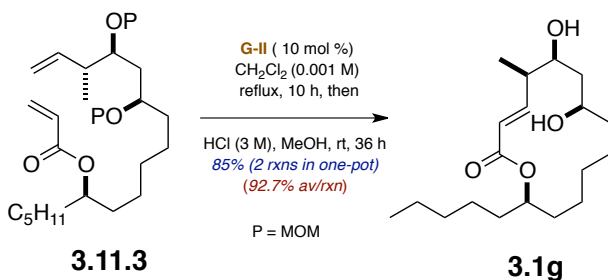
^{13}C NMR (126 MHz, CDCl_3): δ 165.2, 140.4, 131.3, 126.4, 115.2, 96.9, 96.2, 79.1, 77.4, 75.6, 56.0, 55.9, 49.6, 41.5, 36.7, 35.5 (2C), 32.0, 30.0, 26.1, 25.8, 25.1, 22.8, 14.3, 14.0.

HRMS: calculated for $\text{C}_{25}\text{H}_{47}\text{NNaO}_5$ ($\text{M}+\text{Na}$) $^+$ 464.3352; found 464.3362 (TOF MS ES+).

General procedure A; one-pot sequential RCM/MOM-deprotection.

To a flame dried RB was added CH₂Cl₂ (33 mL, 0.001 M), degased it for 20 minutes and was added diene (0.05 mmol) and **G-II** catalyst (10 mol%). The reaction mixture was refluxed for 10–12 h (monitored *via* TLC). After completion of reaction (monitored by TLC), the CH₂Cl₂ was evaporated under reduced pressure. To the crude RCM product was added 2 mL mixture of MeOH and HCl (3.0 M) in a ratio of 1:1.5, respectively. The reaction mixture was stirred at room temperature for 36–40 h (monitored *via* TLC). After completion, the reaction mixture was quenched with aqueous NaHCO₃ (pH ~8), extracted with EtOAc (3x10 mL), dried (Na₂SO₄), filtered, concentrated under reduced pressure, and purified using flash chromatography to furnish the desired macrocycles.

(5*R*,6*S*,8*R*,14*R*,*E*)-6,8-dihydroxy-5-methyl-14-pentyloxacyclotetradec-3-en-2-one (3.1g):



Following general procedure A, the compound **3.1g** was synthesized and purified *via* silica gel column chromatography (Hexane/EtOAc 3:2), 15 mg of **3.13.3** (0.031 mmol) generated 9.4 mg of **3.1g** [85% over 2 rxns in one-pot (92.7% av/rxn)] as a colorless viscous liquid.

FTIR (neat): 3400, 2929, 2858, 2358, 1714, 1699, 1456, 1361, 1362 1083, 1037, 987, 869, 719 cm^{-1} .

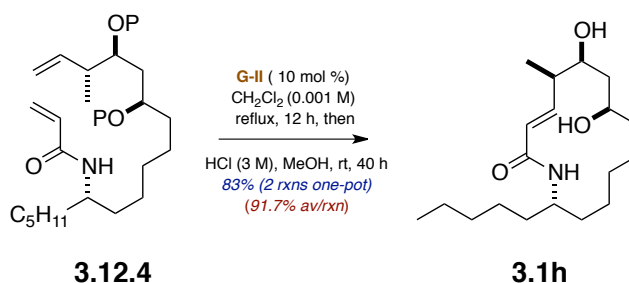
Optical Rotation: $[\alpha]_{\text{D}}^{23} = +10.2$ (c 0.37, CHCl_3).

^1H NMR ^1H NMR (500 MHz, Chloroform- d) δ 6.86 (dd, $J = 15.7, 10.0$ Hz, 1H), 5.87 (d, $J = 15.7$ Hz, 1H), 4.96–4.88 (m, 1H), 4.04–3.94 (m, 2H), 2.84 (bs, 1H), 2.62–2.51 (m, 1H), 2.10–1.98 (m, 1H), 1.84 (dt, $J = 15.5, 4.8$ Hz, 1H), 1.75 – 1.60 (m, 4H), 1.59 – 1.49 (m, 2H), 1.47–1.40 (m, 2H), 1.40 – 1.24 (m, 11H), 1.18 (d, $J = 6.9$ Hz, 3H), 0.90 (t, $J = 5.5$ Hz, 3H).

^{13}C NMR (126 MHz, CDCl_3): δ 166.3, 150.4, 123.2, 75.7, 71.7, 69.4, 43.6, 36.7, 35.5, 35.4, 33.4, 31.9, 28.0, 25.3, 24.7, 23.7, 22.8, 14.3, 13.6.

HRMS: calculated for $\text{C}_{19}\text{H}_{34}\text{NaO}_4$ ($\text{M}+\text{Na}$) $^+$ 349.2355; found 349.2577 (TOF MS ES+).

(5*R*,6*S*,8*R*,14*S*,*E*)-6,8-dihydroxy-5-methyl-14-pentylazacyclotetradec-3-en-2-one (3.1h):



Following general procedure A, the compound **3.1h** was synthesized and purified *via* silica gel column chromatography (Hexane/EtOAc 1:1), 25 mg of **3.12.4** (0.031 mmol) generated 13 mg of **3.1g** [83% over 2 rxns in one-pot (91.7% av/rxn)] as a semi solid.

FTIR (neat): 3330, 3286, 2925, 2850, 1662, 1627, 1558, 1541, 1456, 1436, 1269, 1107, 1078, 983, 869 cm^{-1} .

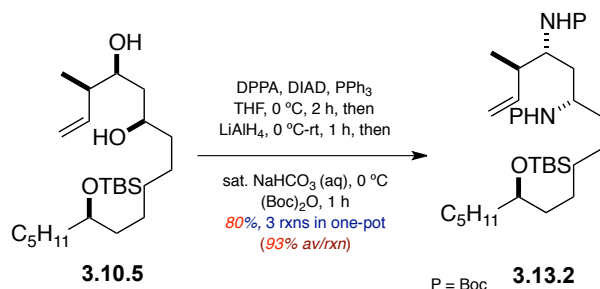
Optical Rotation: $[\alpha]_{\text{D}}^{23} = +3.6$ (c 0.25, CHCl_3).

^1H NMR (400 MHz, MeOD): δ 6.64 (dd, $J = 15.6, 9.5$ Hz, 1H), 5.92 (d, $J = 15.6$ Hz, 1H), 3.92–3.80 (m, 2H), 3.77–3.68 (m, 1H), 2.38–2.28 (m, 1H), 1.76–1.60 (m, 2H), 1.48–1.12 (m, 18H), 1.09 (d, $J = 6.7$ Hz, 3H), 0.83 (t, $J = 6.8$ Hz, 3H).

^{13}C NMR (126 MHz, CDCl_3): δ 166.7, 147.0, 124.9, 73.6, 68.6, 56.1, 53.6, 49.2, 44.1, 35.8, 35.3, 33.0, 31.8, 29.9, 26.0, 23.9, 22.8, 15.5, 14.3.

HRMS: calculated for $\text{C}_{19}\text{H}_{35}\text{NNaO}_3$ ($\text{M}+\text{Na}$) $^+$ 348.2515; found 348.2515 (TOF MS ES $^+$).

di-*tert*-butyl ((3*R*,4*R*,6*S*,12*R*)-12-((*tert*-butyldimethylsilyl)oxy)-3-methylhepta-dec-1-ene-4,6-diyl)dicarbamate (3.13.2):



To a solution of TBS-protected alcohol **3.10.5** (200 mg, 0.48 mmol) in THF (4.8mL, 0.1 M) was added PPh₃ (253 mg, 0.96 mmol) and DIAD (290 mg, 1.44 mmol) under argon atmosphere. The reaction mixture was stirred for 5 min at room temperature and was added DPPA (462 mg, 1.68 mmol) at 0 °C. The reaction mixture was stirred at the same temperature for 2 h (monitored by TLC). After completion of reaction, LiAlH₄ (72.2 mg, 1.92 mmol) was added in portions at 0 °C over 5 minutes and the reaction

mixture was stirred at the same temperature for 1 h (monitored *via* TLC, the azide was reduced to the corresponding amine). After complete consumption of the starting material the reaction mixture was quenched with aq. saturated NaHCO₃ solution (1 mL), stirred for 15 min at 0 °C and diluted with THF (1.2 mL). To the crude reaction mixture were added Boc₂O (230 mg, 1.05 mmol) and the reaction mixture was stirred for 1 h at room temperature. After completion of reaction indicated by TLC, the reaction mixture was quenched with NH₄Cl, extracted with EtOAc (3x30 mL), dried (Na₂SO₄) and concentrated under reduced pressure. The compound was purified using silica gel chromatography (Hexane/EtOAc 4:1), which afforded the Boc-protected alkene **3.13.2** (238 mg, 80% over three reaction one-pot, 93% av/rxn) as colorless viscous liquid.

FTIR (neat): 3338, 2956, 2929, 2856, 1716, 1699, 1506, 1456, 1365, 1249, 1174, 1080, 835, 773 cm⁻¹.

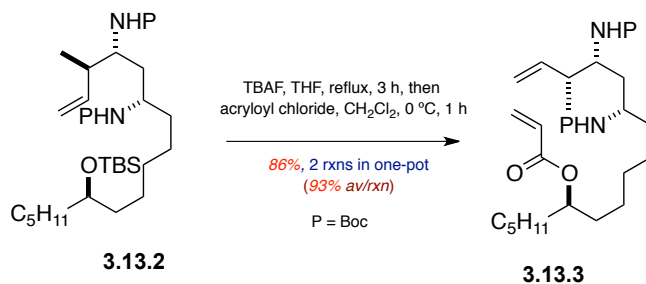
Optical Rotation: $[\alpha]_D^{23} = +13.0$ (*c* 0.4, CHCl₃).

¹H NMR (500 MHz, Chloroform-*d*): δ 5.66 (ddd, *J* = 17.0, 10.3, 8.4 Hz, 1H), 5.19 – 4.94 (m, 2H), 4.65–4.53 (m, 1H), 3.61 (p, *J* = 5.7 Hz, 1H), 3.58–3.46 (m, 2H), 2.45–2.35 (m, 1H), 1.51 – 1.36 (m, 27H), 1.36 – 1.20 (m, 10H), 1.02 (d, *J* = 6.9 Hz, 3H), 0.89 (d, *J* = 2.3 Hz, 12H), 0.04 (s, 3H), 0.03 (s, 3H).

¹³C NMR (126 MHz, CDCl₃): δ 155.8, 140.9, 115.9, 79.3, 79.1, 72.6, 51.8, 48.4, 42.9, 37.32, 37.28, 36.5, 35.5, 32.3, 30.0, 28.7 [3x2C, NHC(O)OC(CH₃)₃], 26.5, 26.2 [3xC, Si-C(CH₃)₃], 25.5, 25.2, 22.9, 18.4, 17.0, 14.3, -4.17, -4.19 [2xC, Si(CH₃)₂].

HRMS: calculated for C₃₄H₆₈N₂NaO₅Si (M+Na)⁺ 635.4795; found 635.4799 (TOF MS ES+).

(6*R*,12*S*,14*R*,15*R*)-12,14-bis((*tert*-butoxycarbonyl)amino)-15-methylheptadec-16-en-6-yl acrylate (3.13.3):



To a stirred solution of TBS-protected alcohol **3.13.2** (200 mg, 0.32) in dry THF (3.2 mL, 0.1 M) under argon was added TBAF (183 mL, 0.65 mmol) at room temperature. The reaction mixture was refluxed for 3 h. After completion (monitored via TLC), the solvent was evaporated and CH₂Cl₂ (3.2 mL, 0.1 M) was added under argon followed by Et₃N (269 μ L, 1.92 mmol) and DMAP (4.06 mg, 0.032 mmol). The crude reaction mixture was cooled to 0 $^\circ$ C and added acryloyl chloride (72 μ L, 0.8 mmol) drop wise and the reaction mixture was stirred at 0 $^\circ$ C for 1 h. After completion of reaction, it was quenched with ice cold water, the organic layer was extracted with CH₂Cl₂ (3x20 mL), dried (Na₂SO₄), concentrated and purified using silica gel chromatography (Hexane/EtOAc 5:1), which furnished the acrylate **3.13.3** (156 mg, 86 % over two reactions one-pot, 93% av/rxn) as colorless liquid.

FTIR (neat): 3365, 2931, 2860, 2360, 1716, 1699, 1519, 1506, 1456, 1390, 1245, 1191, 1174, 1047, 985, 773 cm⁻¹.

Optical Rotation: $[\alpha]_D^{23} = +10.0$ (*c* 0.25, CHCl₃).

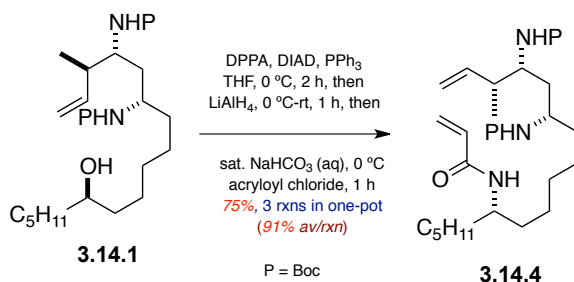
¹H NMR (500 MHz, Chloroform-*d*): δ 6.39 (dd, *J* = 17.3, 1.5 Hz, 1H), 6.12 (dd, *J* = 17.3, 10.4 Hz, 1H), 5.81 (dd, *J* = 10.4, 1.6 Hz, 1H), 5.66 (ddd, *J* = 17.1, 10.3, 8.4 Hz,

1H), 5.11 – 5.01 (m, 2H), 4.94 (p, $J = 6.5$ Hz, 1H), 4.65–4.49 (m, 1H), 3.59–3.43 (m, 2H), 2.44–2.31 (m, 1H), 1.62–1.52 (m, 3H), 1.49–1.37 (m, 23H), 1.28 (m, 13H), 1.02 (d, $J = 6.8$ Hz, 3H), 0.88 (t, $J = 6.7$ Hz, 3H).

^{13}C NMR (126 MHz, CDCl_3): δ 166.3, 155.9, 155.8, 140.8, 130.4, 129.2, 115.9, 79.3, 79.1, 74.7, 51.8, 48.4, 42.9, 36.5, 35.4, 34.3, 34.3, 31.9, 29.5, 28.7 [3x2C, $\text{NHC(O)OC}(\text{CH}_3)_3$], 26.3, 25.5, 25.2, 22.7, 17.0, 14.2.

HRMS: calculated for $\text{C}_{31}\text{H}_{56}\text{N}_2\text{NaO}_6$ ($\text{M}+\text{Na}$) $^+$ 635.4795; found 635.4799 (TOF MS ES+).

di-*tert*-butyl ((3*R*,4*R*,6*S*,12*S*)-12-acrylamido-3-methylheptadec-1-ene-4,6-diyl) dicarbamate (3.14.4):



To a solution of Boc-protected alcohol **3.14.1** (100 mg, 0.20 mmol) in THF (2.0 mL, 0.1 M) was added PPh_3 (5.2 mg, 0.02 mmol) and DIAD (80 mg, 0.40 mmol). The reaction mixture was stirred for 5 min at room temperature and then was added DPPA (115 mg, 0.42 mmol) at 0°C . The reaction mixture was stirred at the same temperature for 2 h (monitored by TLC). After completion of reaction, LiAlH_4 (22.8 mg, 0.6 mmol) was added in portions at 0°C over 5 minutes and the reaction mixture was stirred at the same temperature for 1 h (monitored *via* TLC, the azide was reduced to the corresponding amine). After complete consumption of the starting material, the reaction

mixture was quenched with aq. saturated NaHCO₃ solution (0.8 mL), stirred for 15 min at 0 °C and diluted with THF (1.2 mL). Acryloyl chloride (39.8 µl, 0.44 mmol) was added at the same temperature and the reaction mixture was stirred for 1 hour. After completion of reaction indicated by TLC, the reaction mixture was quenched with NH₄Cl, extracted with EtOAc (20x3 mL), dried (Na₂SO₄) and concentrated under reduced pressure. The compound was purified using silica gel chromatography (Hexane/EtOAc 4:1), which afforded the acrylamide **3.14.4** (82mg, 75% over three reactions in one-pot, 91% av/rxn) as colorless viscous liquid.

FTIR (neat): 3307, 2929, 2854, 2356, 1699, 1539, 1519, 1456, 1363, 1244, 1172, 895, 912 cm⁻¹.

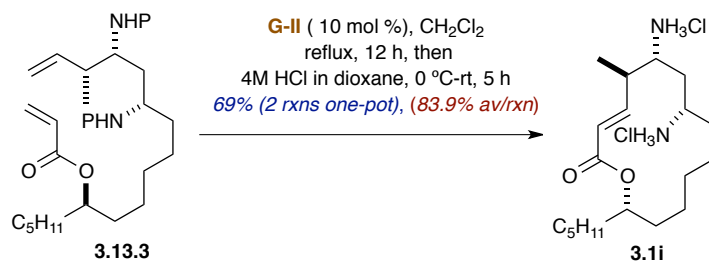
Optical Rotation: $[\alpha]_D^{23} = +9.1$ (*c* 0.25, CHCl₃).

¹H NMR (500 MHz, Chloroform-*d*) δ 6.21 (dd, *J* = 17.0, 1.5 Hz, 1H), 6.03 (dd, *J* = 16.9, 10.2 Hz, 1H), 5.68–5.49 (m, 2H), 5.23 (bs, 1H), 5.07–4.87 (m, 2H), 4.67–4.50 (m, 1H), 3.99–3.86 (m, 1H), 3.50–3.37 (m, 2H), 2.38–2.25 (m, 1H), 1.61–1.47 (m, 4H), 1.43–1.31 (m, 16H), 1.28–1.16 (m, 18H), 0.94 (d, *J* = 6.8 Hz, 3H), 0.88 (t, *J* = 6.7 Hz, 3H).

¹³C NMR (126 MHz, CDCl₃): δ 165.3, 156.0, 140.9, 131.4, 126.4, 122.5, 115.9, 79.3 (2C), 79.1, 51.7, 49.6, 48.3, 42.9, 35.55, 35.48, 35.1, 32.0, 29.5, 28.7 [3x2C, NHC(O)OC(CH₃)₃], 26.0, 25.9, 25.8, 22.8, 16.9, 14.3.

HRMS: calculated for C₃₁H₅₇N₃NaO₅ (M+Na)⁺ 635.4795; found 635.4799 (TOF MS ES+).

(5*R*,6*R*,8*S*,14*R*,*E*)-6,8-diamino-5-methyl-14-pentyloxacyclotetradec-3-en-2-one (Salt) (3.1i):



To a flame dried RB was added CH_2Cl_2 (38 mL, 0.001 M), degased it for 20 minutes and was added diene **3.13.3** (20 mg, 0.038 mmol) followed by **G-II** catalyst (10 mol%). The reaction mixture was refluxed for 12 h (monitored *via* TLC). After completion of RCM reaction, the CH_2Cl_2 was evaporated under reduced pressure. To the crude RCM product was added a cooled solution of HCl (1 mL, 4.0 M in dioxane) and the reaction mixture was stirred at room temperature for 5 h (monitored *via* TLC). After completion of reaction the dioxane was evaporated completely under reduced pressure. A mixture of EtOAc:heptane (6 mL, 1:4 ratio) was added to the above residue and stirred it at room temperature for 30 min. The reaction mixture was filtered and the resulting solids was washed with the same mixture of solvents (3 mL) and the compound was dried at 40–45 °C for 5-6 h, which afforded 7.1 mg of pure amine salt **3.1i** in 69% yield (83.9% av/rxn, three reactions one-pot) as a pale yellow solid.

FTIR (neat): 3433, 2929, 2854, 1708, 1602, 1521, 1458, 1265, 1184, 991, 721 cm^{-1} .

Optical Rotation: $[\alpha]_{\text{D}}^{23} = -15.3$ (*c* 0.15, MeOH).

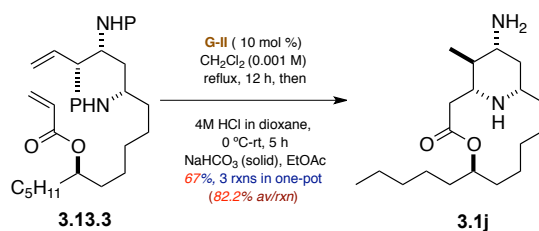
^1H NMR (500 MHz, MeOD): δ 6.74 (dd, $J = 15.7, 9.8$ Hz, 1H), 5.87 (d, $J = 15.7$ Hz, 1H), 4.79–4.73 (m, 1H), 3.50–3.43 (m, 1H), 3.38–3.28 (m, 1H), 2.60–2.50 (m, 1H), 2.04–

1.81 (m, 2H), 1.72–1.60 (m, 1H), 1.58–1.08 (m, 17H), 1.04 (d, $J = 6.5$ Hz, 3H), 0.74–0.67 (m, 3H).

^{13}C NMR (101 MHz, MeOD): δ 165.5, 149.2, 124.0, 74.7, 60.2, 51.1, 40.9, 38.3, 32.9, 31.4, 30.4, 28.6, 25.9, 25.0, 22.7, 22.2, 21.2, 16.9, 12.9.

HRMS: calculated for $\text{C}_{19}\text{H}_{37}\text{N}_2\text{O}_2$ (H^+ for free-salt) 325.2855; found 325.2853 (TOF MS ES+).

(6*R*,12*S*,14*R*,15*R*)-12,14-bis((*tert*-butoxycarbonyl)amino)-15-methylheptadec-16-en-6-yl acrylate (3.1j):



To a flame dried RB was added CH_2Cl_2 (27 mL, 0.001 M), degased it for 20 minutes and was added diene **3.13.3** (15 mg, 0.027 mmol) followed by **G-II** catalyst (10 mol %). The reaction mixture was refluxed for 12 h (monitored *via* TLC). After completion of RCM reaction, the CH_2Cl_2 was evaporated under reduced pressure. To the crude RCM product was added a cooled solution of HCl (1 mL, 4.0 M in dioxane) and the reaction mixture was stirred at room temperature for 5 h (monitored *via* TLC). After completion of reaction, the dioxane was evaporated completely under reduced pressure. To the crude reaction mixture was added EtOAc (10 mL) followed by the addition of solid NaHCO_3 (10 mg) and the reaction mixture was stirred at room temperature for 1 h. The solid NaHCO_3 was removed via filtration using celite® pad and the solid residue was washed with EtOAc (15 mL). The filtrate was evaporated under reduced pressure and the crude product was purified by basic alumina using 8–10%

MeOH in CHCl₃ to furnish the pure cyclic lactone **3.1j** (6 mg) in 67% yield (82.2% av/rxn) as a colorless gummy liquid.

FTIR (neat): 3321, 2921, 2856, 2360, 1724, 1546, 1458, 1265, 1184, 991, 721 cm⁻¹.

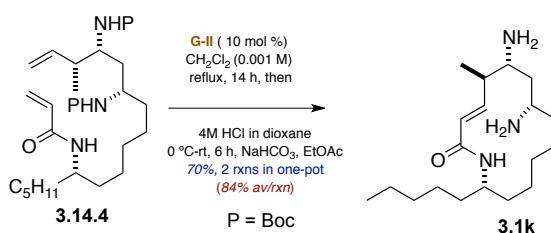
Optical Rotation: $[\alpha]_D^{23} = -15.3$ (*c* 0.15, MeOH).

¹H NMR (400 MHz, MeOD): δ 4.93–4.85 (m, 1H), 3.29 (dt, *J* = 12.7, 4.6 Hz, 1H), 2.92 (t, *J* = 10.9 Hz, 1H), 2.74 (td, *J* = 11.3, 4.2 Hz, 1H), 2.54 (t, *J* = 12.9 Hz, 1H), 2.18 (dd, *J* = 13.1, 4.5 Hz, 1H), 1.93–1.86 (m, 1H), 1.71–1.01 (m, 20H), 0.83 (d, *J* = 6.9 Hz, 3H), 0.75 (t, *J* = 6.7 Hz, 3H).

¹³C NMR (126 MHz, MeOD): δ 173.3, 75.6, 55.7, 50.7, 44.8, 40.6, 40.2, 33.9, 32.4, 31.8, 31.4, 28.2, 25.3, 24.0, 22.6, 22.2, 21.1, 13.6, 13.0.

HRMS: calculated for C₁₉H₃₇N₂O₂ (H⁺ for free-salt) 325.2855; found 325.2854 (TOF MS ES+).

(5*R*,6*R*,8*S*,14*S*,*E*)-6,8-diamino-5-methyl-14-pentylazacyclotetradec-3-en-2-one (3.1k):



To a flame dried RB was added CH₂Cl₂ (34 mL, 0.001 M), degased it for 20 minutes and was added diene **3.14.4** (19 mg, 0.034 mmol) followed by **G-II** catalyst (10 mol %). The reaction mixture was refluxed for 12 h (monitored *via* TLC). After completion of RCM reaction, the CH₂Cl₂ was evaporated under reduced pressure. To the crude RCM product was added a cold solution of HCl (1 mL, 4.0 M in dioxane) and the

reaction mixture was stirred at room temperature for 6 h (monitored *via* TLC). After completion of reaction, the dioxane was evaporated completely under reduced pressure. To the crude reaction mixture was added EtOAc (6 mL) followed by solid NaHCO₃ (5 mg) and the reaction mixture was stirred at room temperature for 1 h. The solid NaHCO₃ was removed via filtration using celite® pad and washed with EtOAc (8 mL). The filtrate was evaporated under reduced pressure and the crude product was purified using basic alumina using 10% MeOH in CHCl₃ to furnish the pure cyclic lactam **3.1k** (6 mg) in 70% yield (82.2% av/rxn) as a brownish gummy liquid.

FTIR (neat): 3278, 2931, 2858, 1683, 1676, 1438, 1205, 1184, 1137, 842, 800, 723 cm⁻¹.

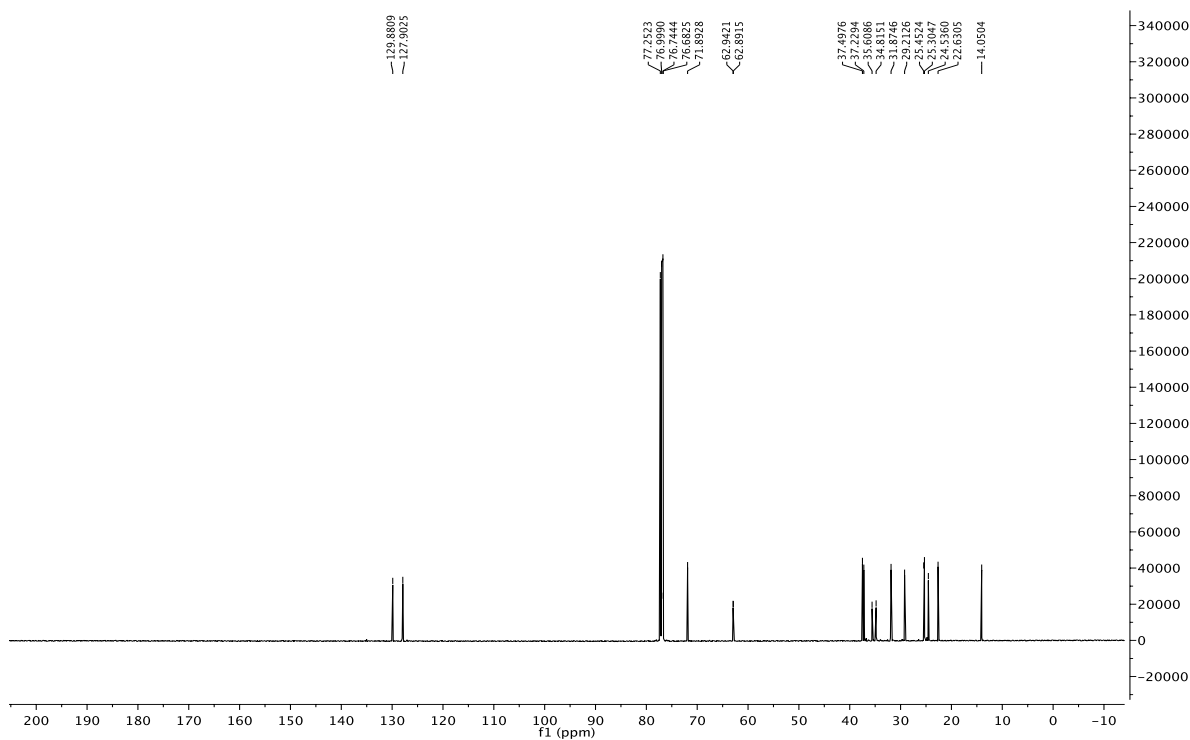
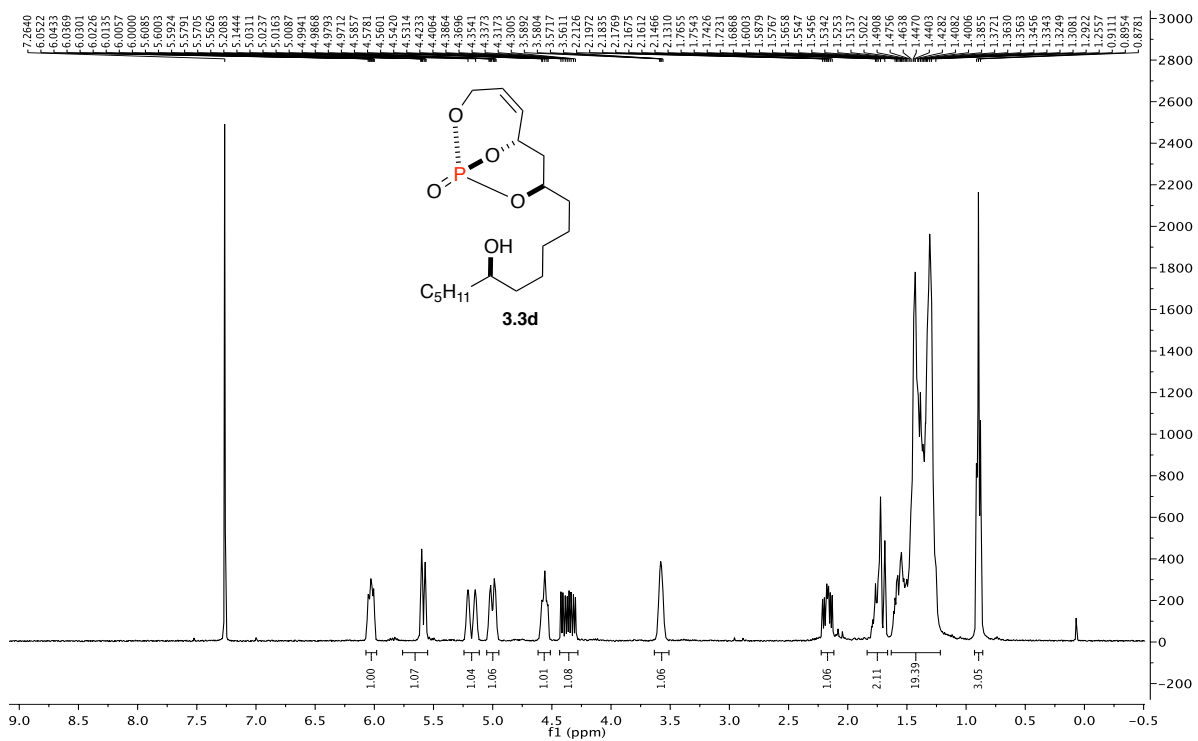
Optical Rotation: $[\alpha]_D^{23} = -9.6$ (*c* 0.25, MeOH).

¹H NMR (500 MHz, Methanol-*d*₄): δ 6.51 (dd, *J* = 15.2, 10.6 Hz, 1H), 6.11 (d, *J* = 15.2 Hz, 1H), 4.11 – 3.91 (m, 1H), 3.49 – 3.35 (m, 1H), 3.17 (dt, *J* = 10.1, 3.4 Hz, 1H), 2.52 – 2.39 (m, 1H), 2.09 – 1.69 (m, 3H), 1.69 – 1.25 (m, 19H), 1.23 (d, *J* = 6.5 Hz, 3H), 1.21 – 1.03 (m, 4H), 0.74 (t, *J* = 6.4 Hz, 3H).

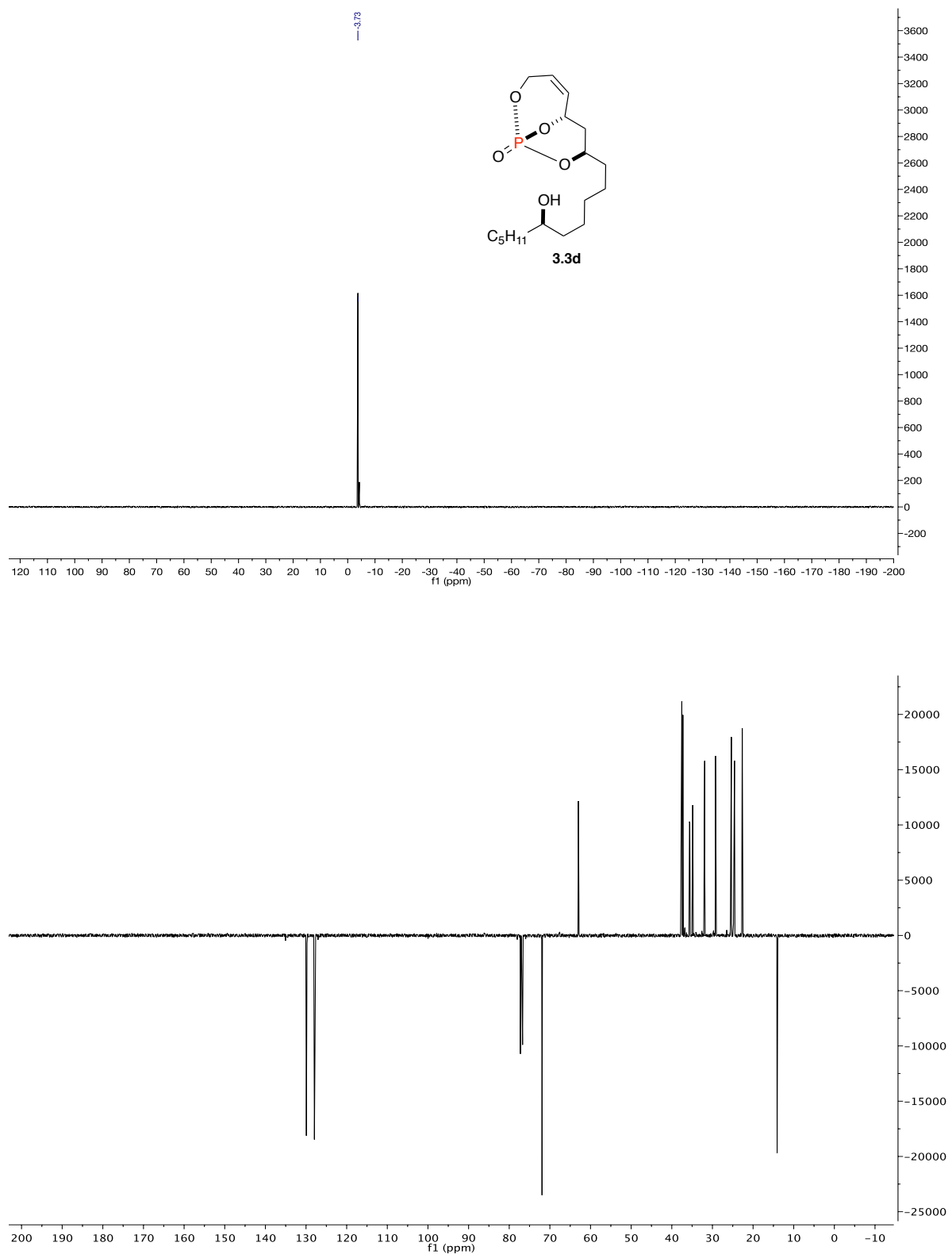
¹³C NMR (126 MHz, MeOD): δ 168.5, 145.9, 127.1, 55.5, 53.1, 42.3, 36.4, 36.1, 35.6, 34.5, 32.9, 30.9, 28.5, 27.2, 26.8, 23.8 (2C), 18.9, 14.5.

HRMS: calculated for C₁₉H₃₈N₃O (H⁺) 324.3015; found 324.3008 (TOF MS ES+).

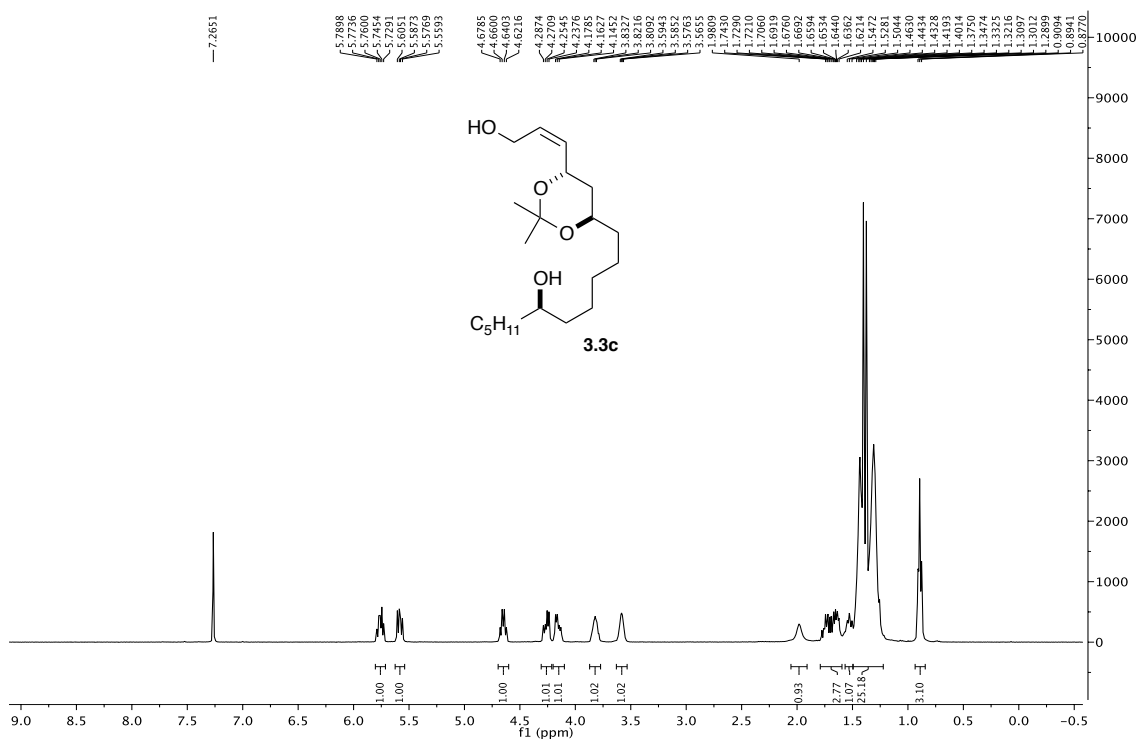
5.2a: A Pot-Economical Approach to the Total synthesis of Sch-725674 (Chapter 3)
(6*S*,8*R*)-8-((*R*)-6-hydroxyundecyl)-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-ene-1-oxide (3.3d):



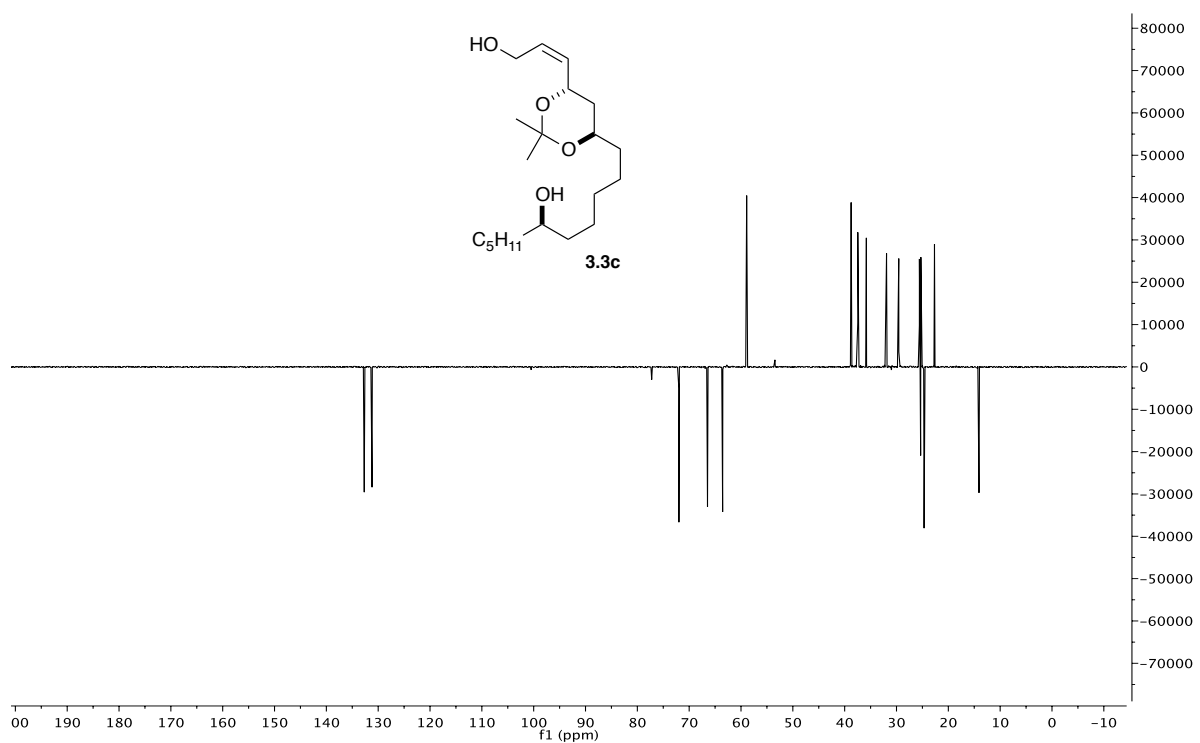
(6*S*,8*R*)-8-((*R*)-6-hydroxyundecyl)-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-ene-1-oxide (3.3d):



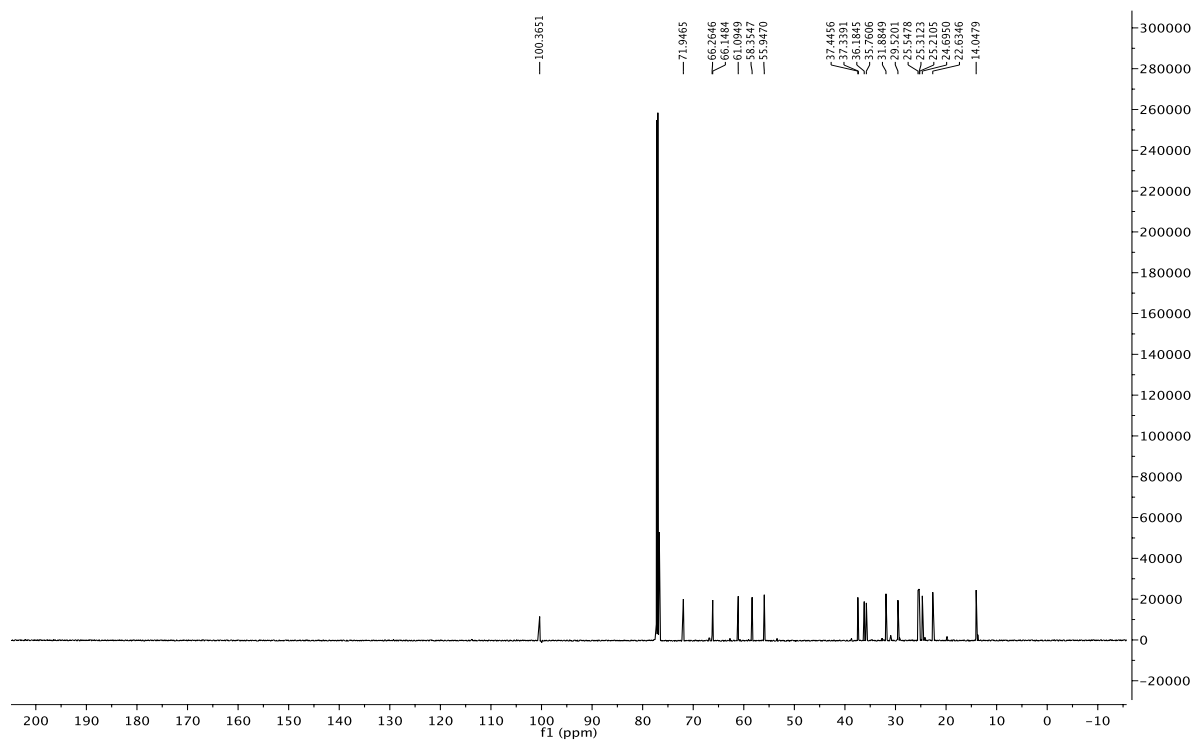
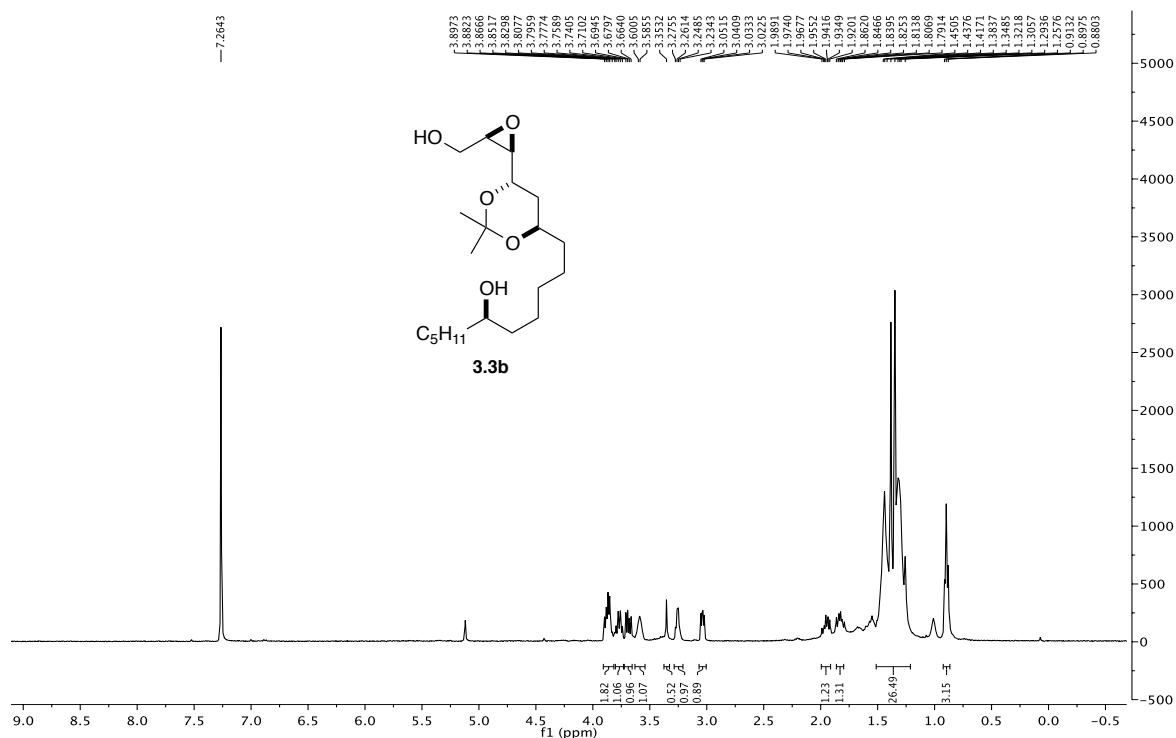
(*R*)-1-((4*R*,6*S*)-6-((*Z*)-3-Hydroxyprop-1-en-1-yl)-2,2-dimethyl-1,3-dioxan-4-yl)undecan-6-ol (3.3c):



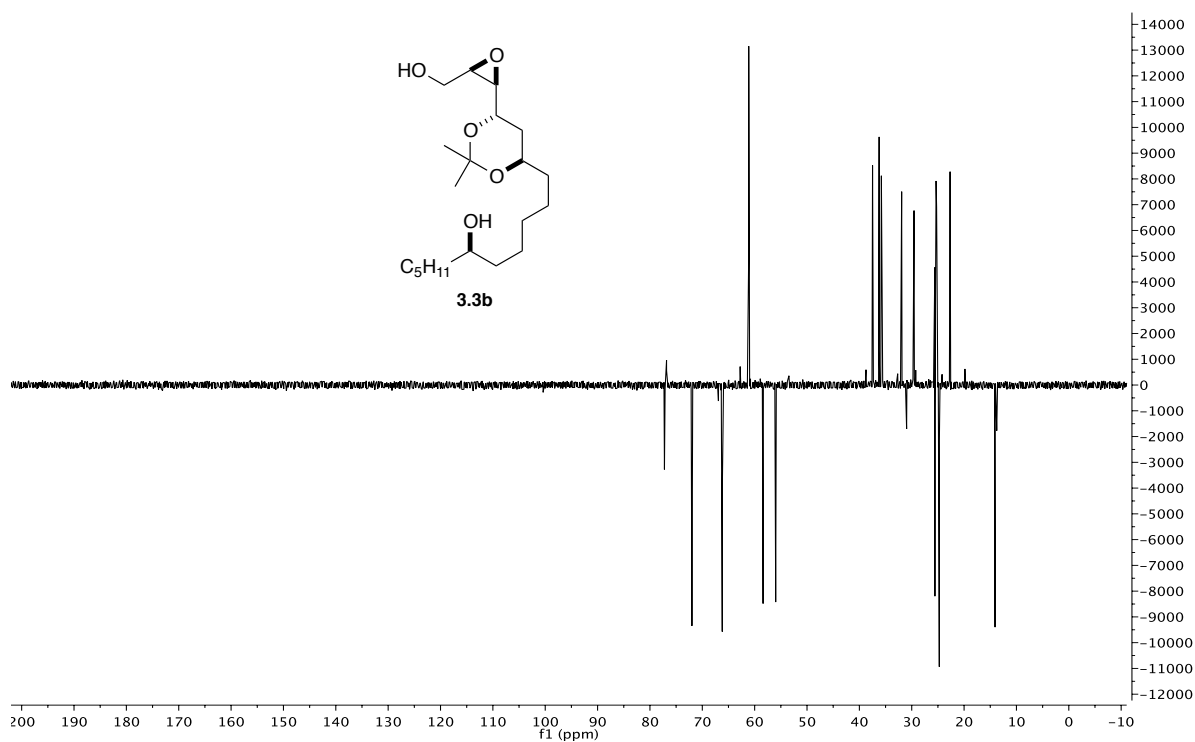
(*R*)-1-((4*R*,6*S*)-6-((*Z*)-3-Hydroxyprop-1-en-1-yl)-2,2-dimethyl-1,3-dioxan-4-yl)undecan-6-ol (3.3c):



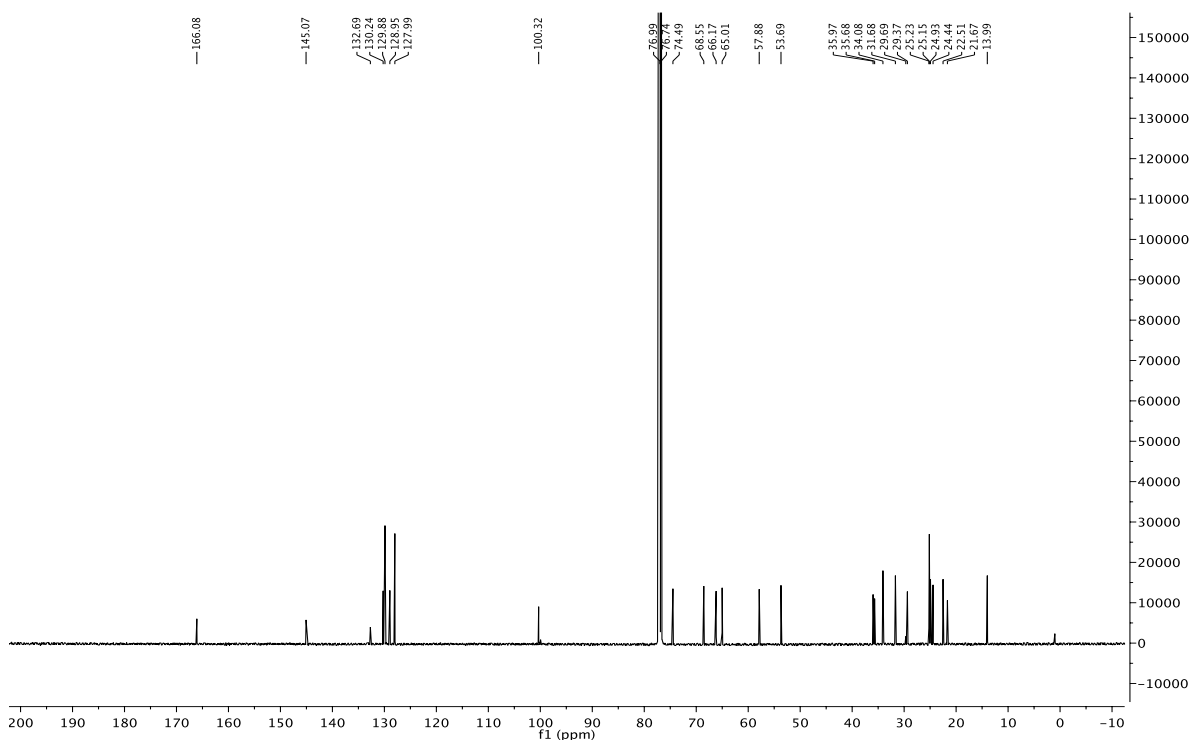
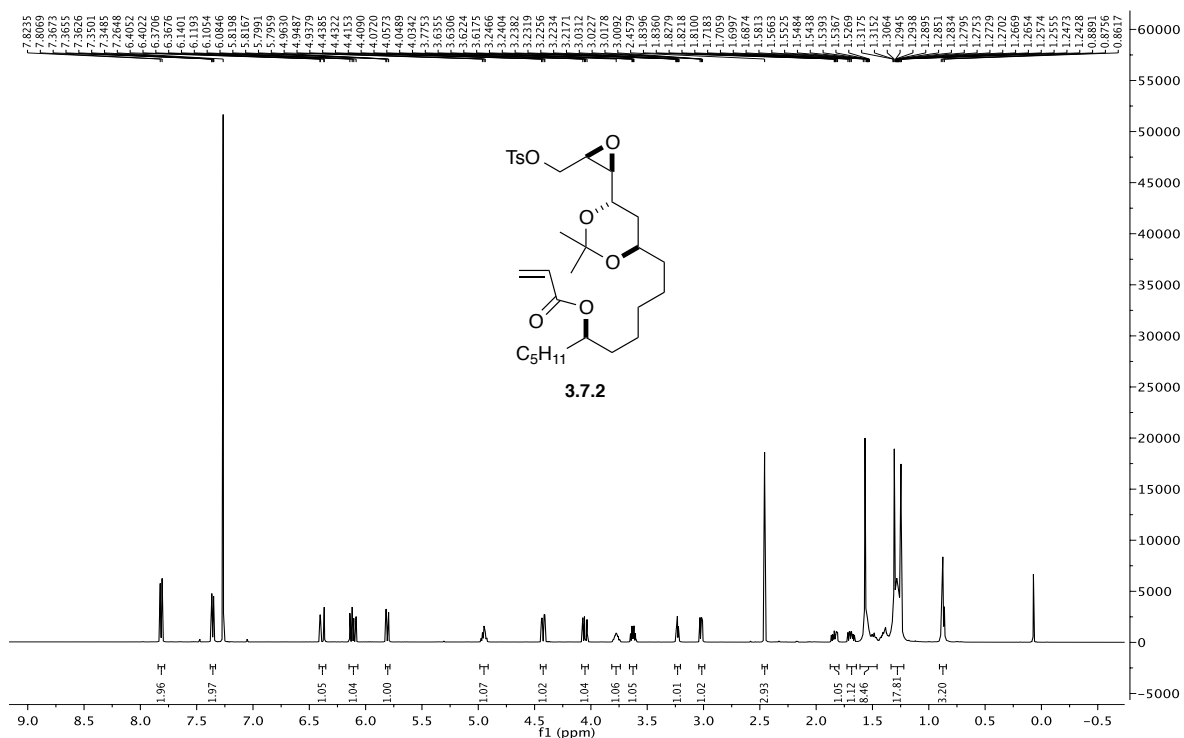
(*R*)-1-((4*R*,6*S*)-6-((2*S*,3*R*)-3-(hydroxymethyl)oxiran-2-yl)-2,2-dimethyl-1,3-dioxan-4-yl)undecan-6-ol (3.3b):



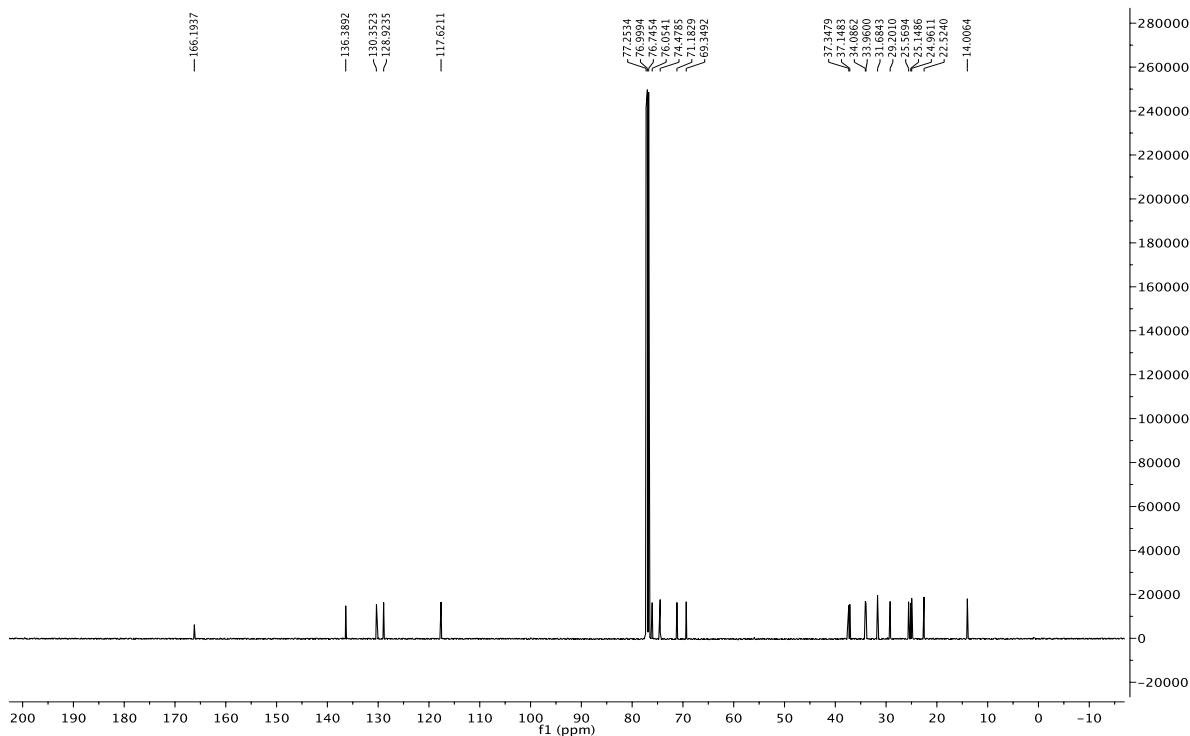
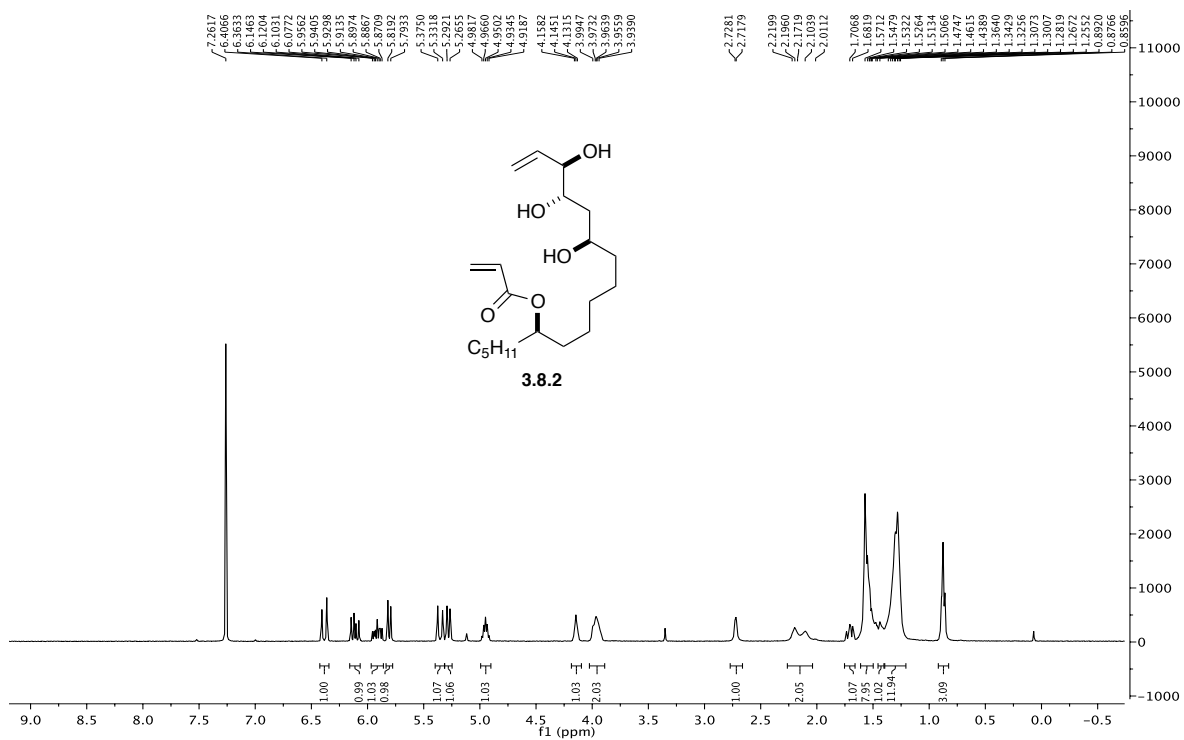
(*R*)-1-((4*R*,6*S*)-6-((2*S*,3*R*)-3-(hydroxymethyl)oxiran-2-yl)-2,2-dimethyl-1,3-dioxan-4-yl)undecan-6-ol (3.3b):



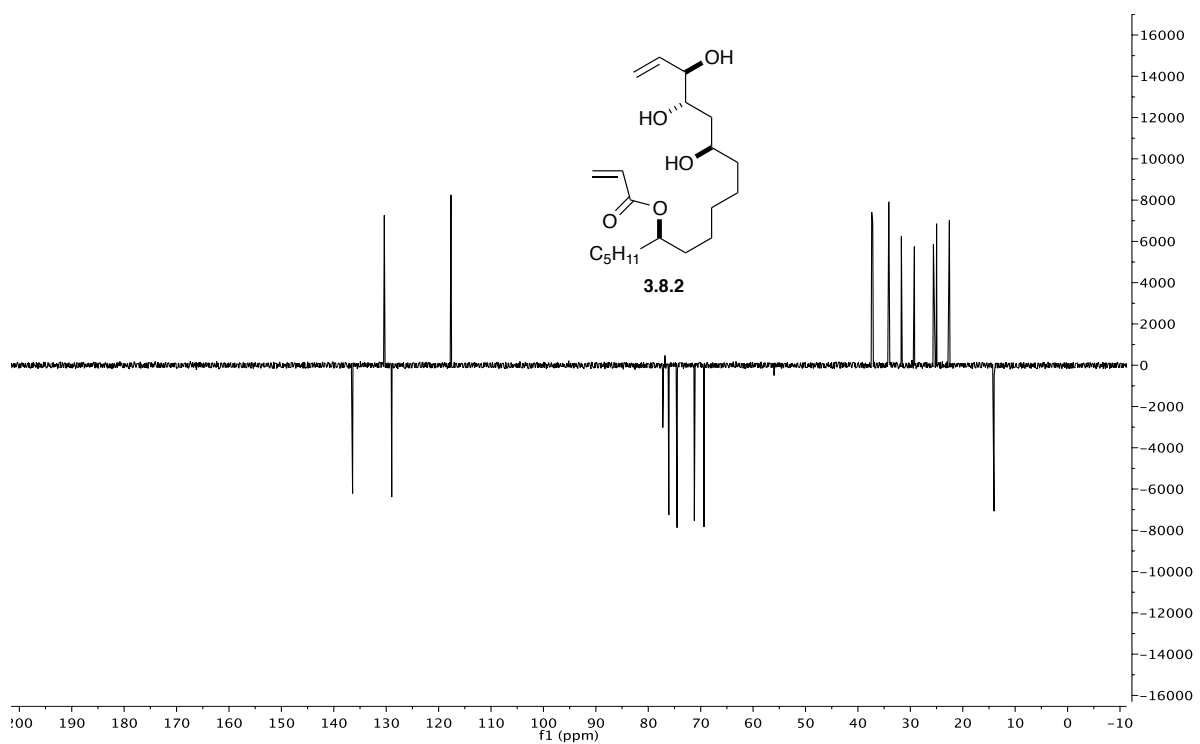
(*R*)-1-((4*R*,6*S*)-2,2-dimethyl-6-((2*S*,3*R*)-3-((tosyloxy)methyl)oxiran-2-yl)-1,3-dioxan-4-yl)undecan-6-yl acrylate (3.7.2):



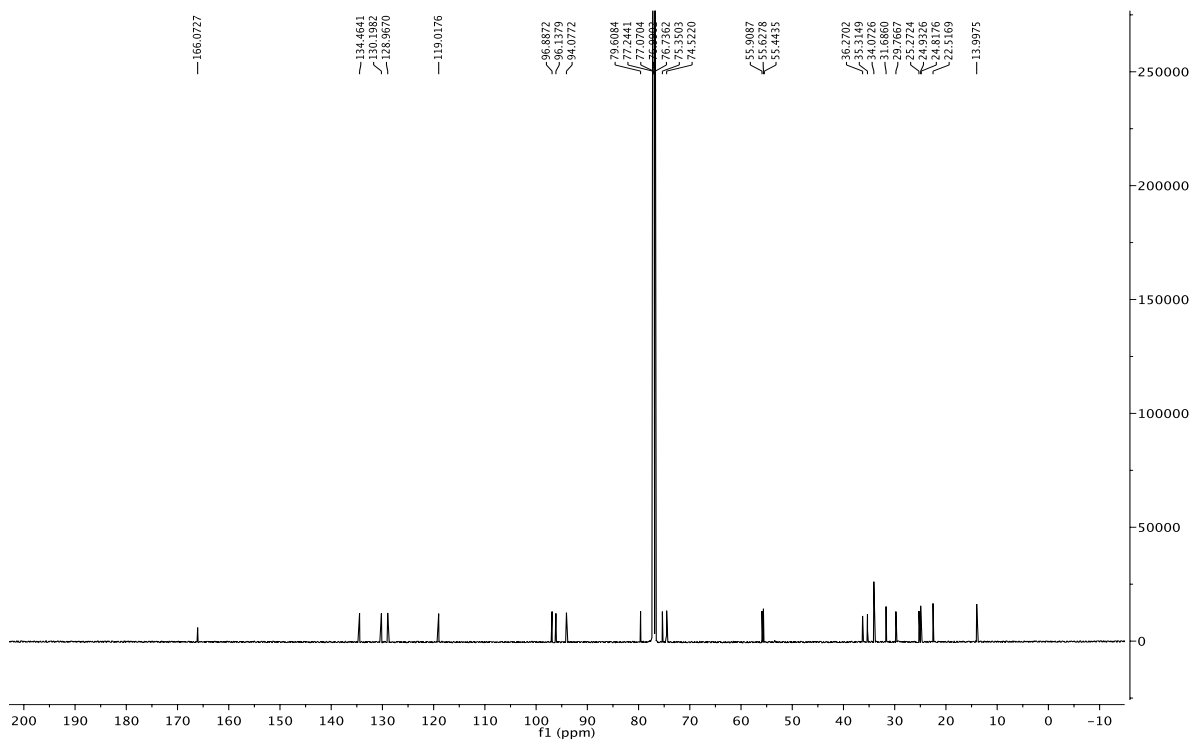
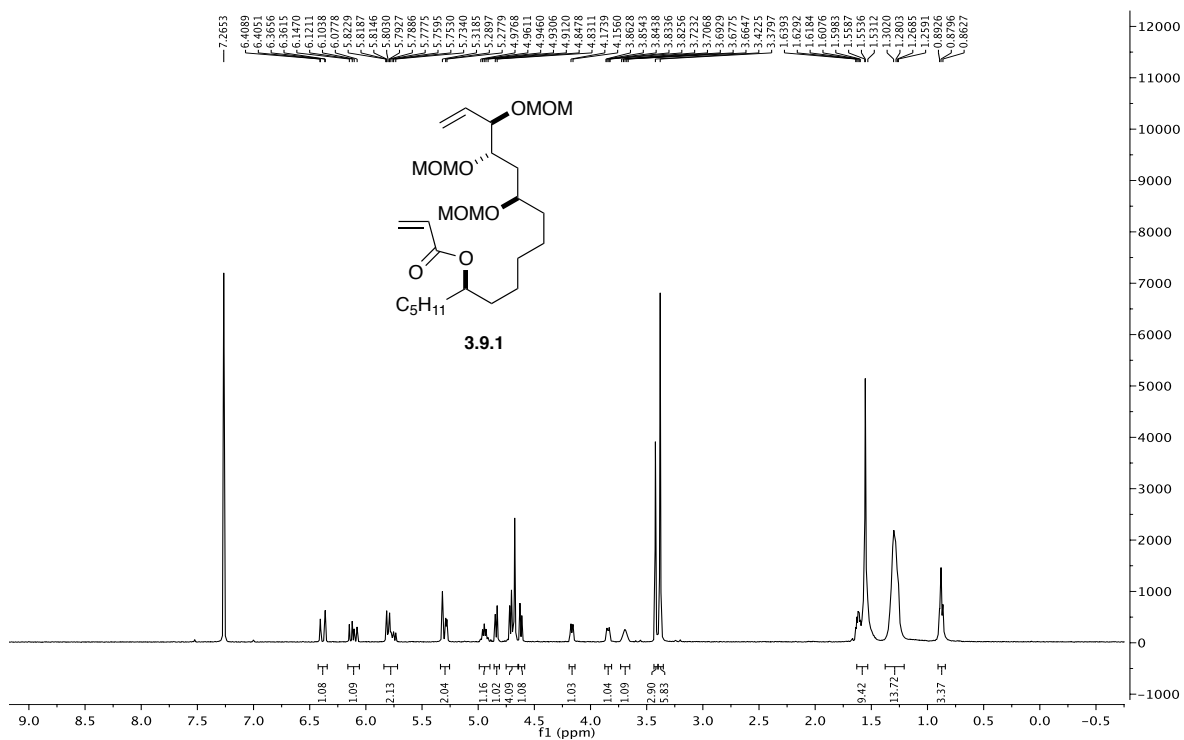
(6*R*,12*R*,14*S*,15*R*)-12,14,15-Trihydroxyheptadec-16-en-6-yl acrylate (3.8.2):



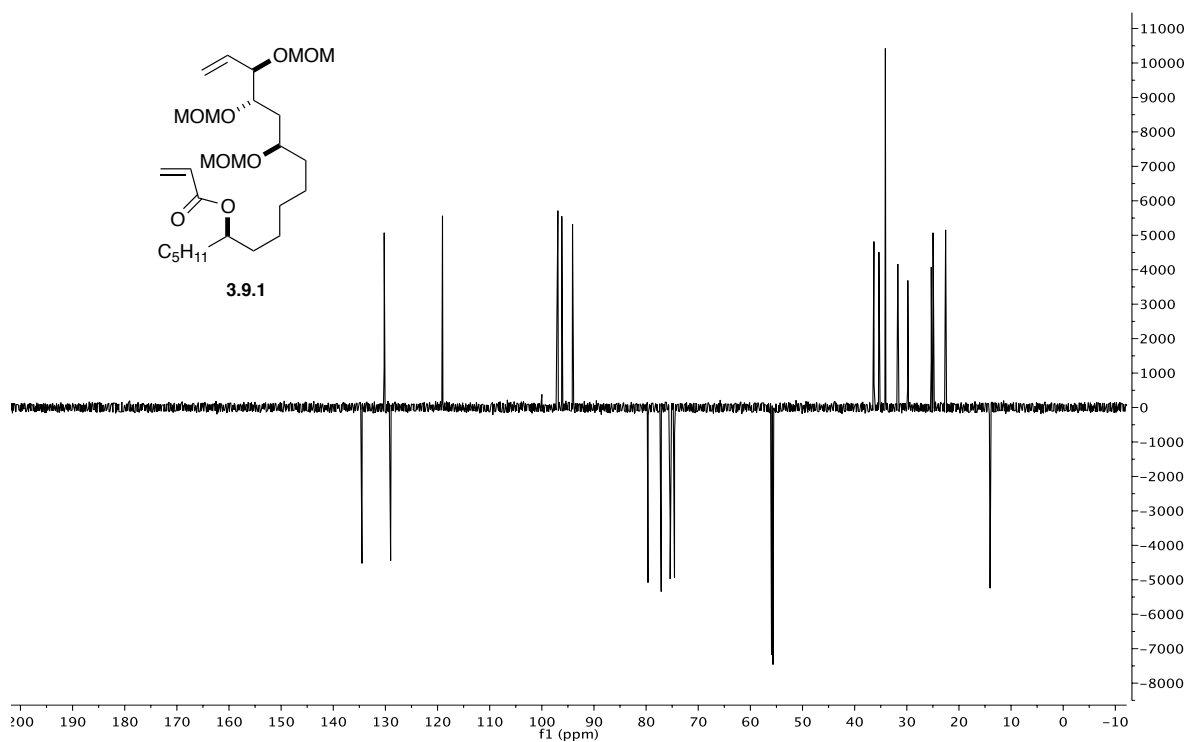
(6*R*,12*R*,14*S*,15*R*)-12,14,15-Trihydroxyheptadec-16-en-6-yl acrylate (3.8.2)



**(6*R*,12*R*,14*S*,15*R*)-12,14,15-tris(Methoxymethoxy)heptadec-16-en-6-yl acrylate
(3.9.1)**



**(6*R*,12*R*,14*S*,15*R*)-12,14,15-tris(Methoxymethoxy)heptadec-16-en-6-yl acrylate
(3.9.1)**



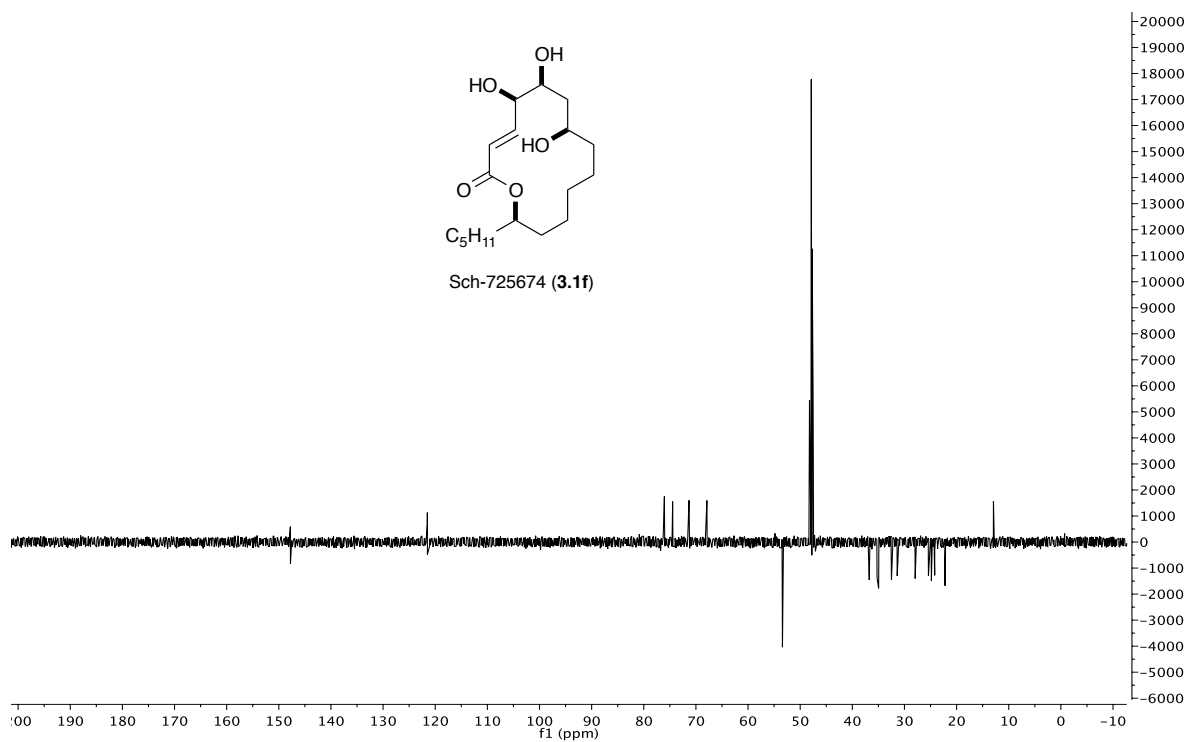
Chemical structure of **Sch-725674 (3.1f)** is shown as an inset. The structure is a 12-membered ring containing two hydroxyl groups, a ketone, and a C_5H_{11} substituent.

¹H NMR spectrum (CDCl₃) data:

Chemical Shift (ppm)	Integration
6.8972, 6.8820, 6.8576, 6.8426	1.03
6.1027, 6.0989, 6.0852, 6.0594	1.00
4.9755, 4.9693, 4.9535, 4.9487, 4.9369, 4.9205, 4.8858, 4.8800	1.08
4.4848, 4.4805, 4.4771, 4.4737, 4.4720	0.94
4.0033, 3.9875, 3.9731, 3.8662, 3.8483, 3.8469, 3.8358	1.06, 0.91
1.8533, 1.8385, 1.8315, 1.8171, 1.8019, 1.7304, 1.6942, 1.6790, 1.6636, 1.6539, 1.6424, 1.6288, 1.6173, 1.6078, 1.5952, 1.5734, 1.5576, 1.5192, 1.4945, 1.4287, 1.4237, 1.3983, 1.3724, 1.3166, 1.2922, 1.2587, 1.2483, 1.2363, 1.2096, 1.1946, 1.1895, 1.1778, 1.1748, 1.1600, 1.0924, 0.8854	1.11, 5.38, 10.92, 3.17, 3.16

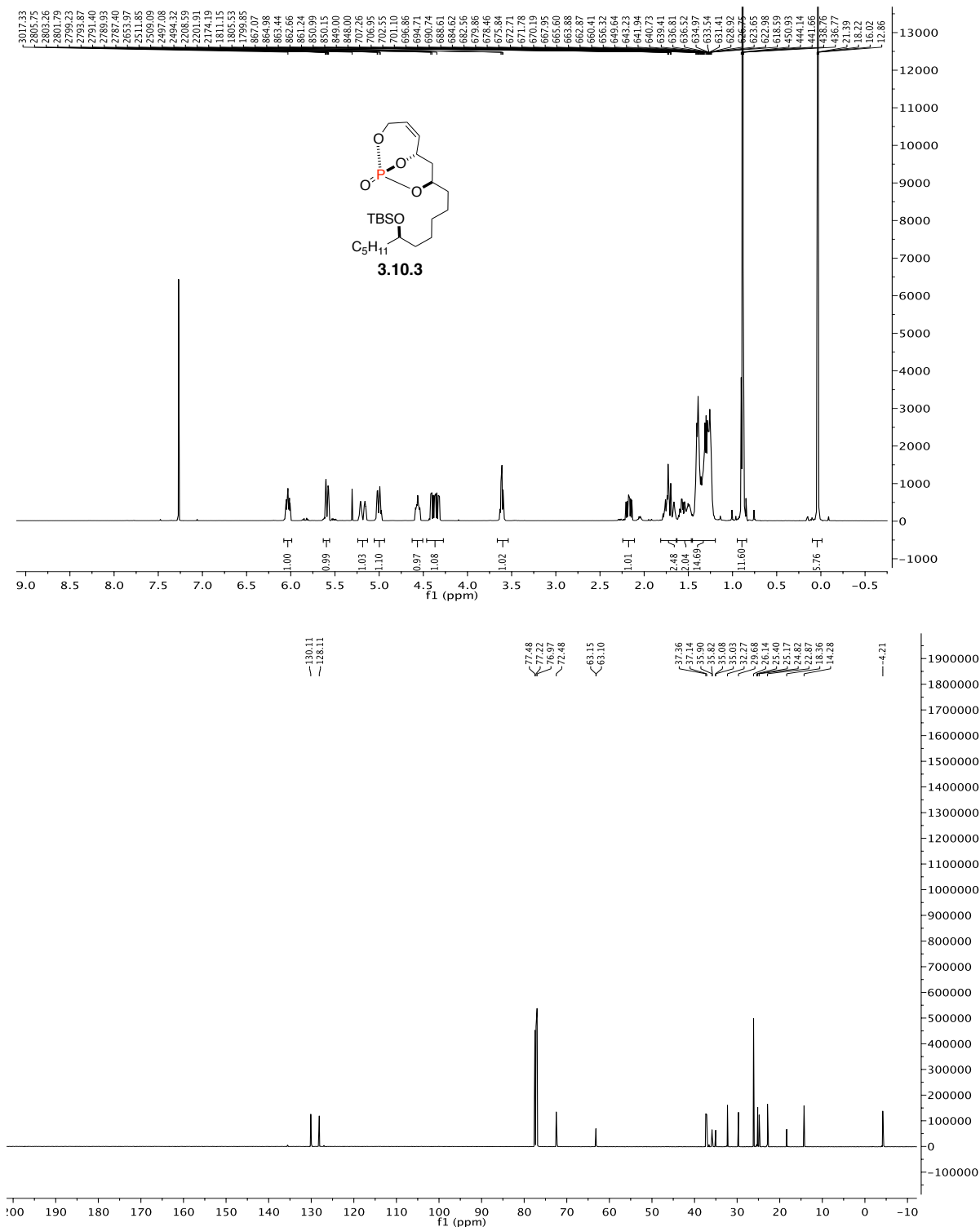


(5*R*,6*S*,8*R*,14*R*,*E*)-5,6,8-Trihydroxy-14-pentyloxacyclotetradec-3-en-2-one (3.1f)

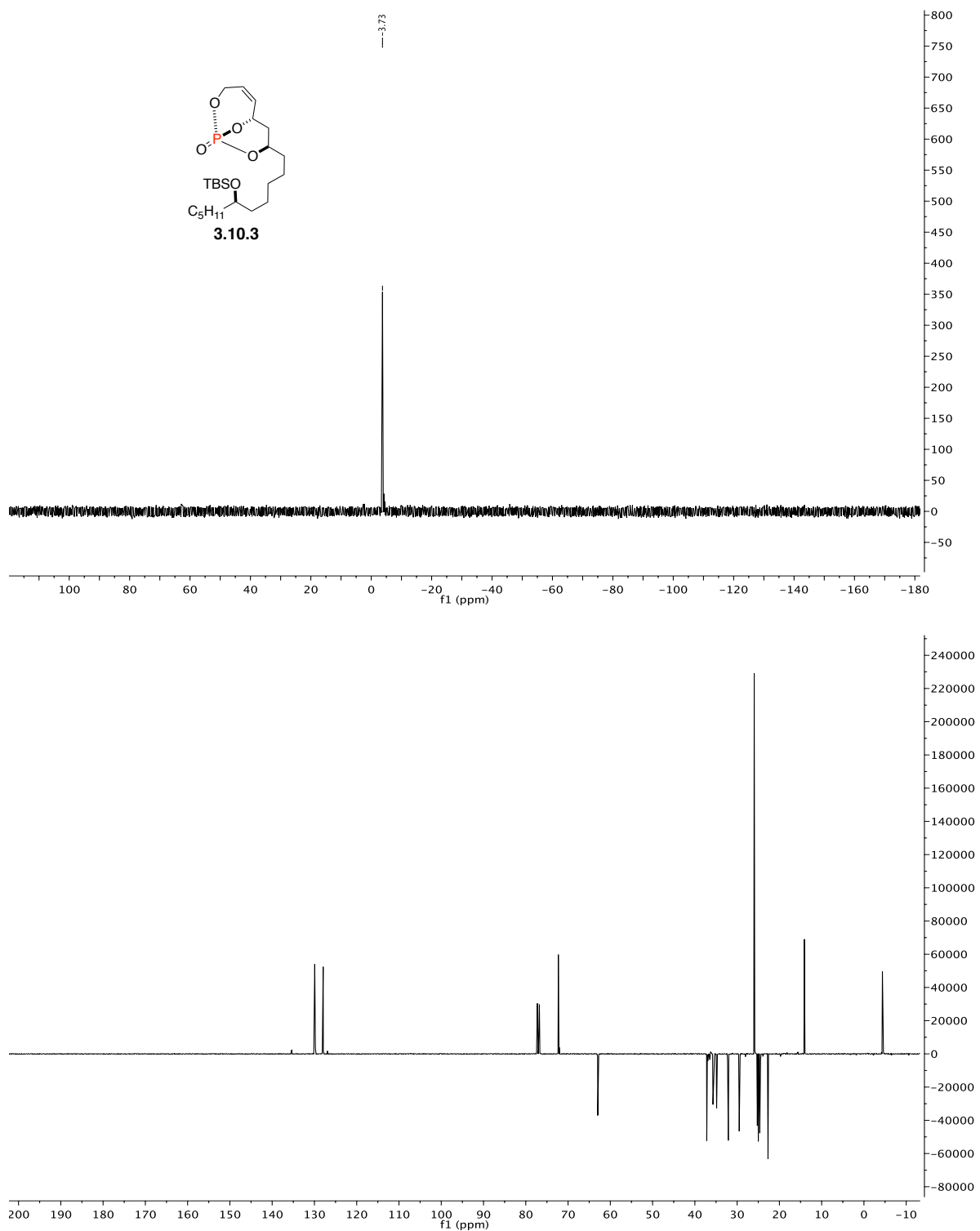


5.2b: 5.2b: A pot-economical approach for the total syntheses of Sch-725674 analogs (Chapter-3)

(1*S*,6*S*,8*R*)-8-((*R*)-6-((*tert*-butyldimethylsilyl)oxy)undecyl)-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-ene 1-oxide (3.10.3):



(1*S*,6*S*,8*R*)-8-((*R*)-6-((*tert*-butyldimethylsilyl)oxy)undecyl)-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-ene 1-oxide (3.10.3):



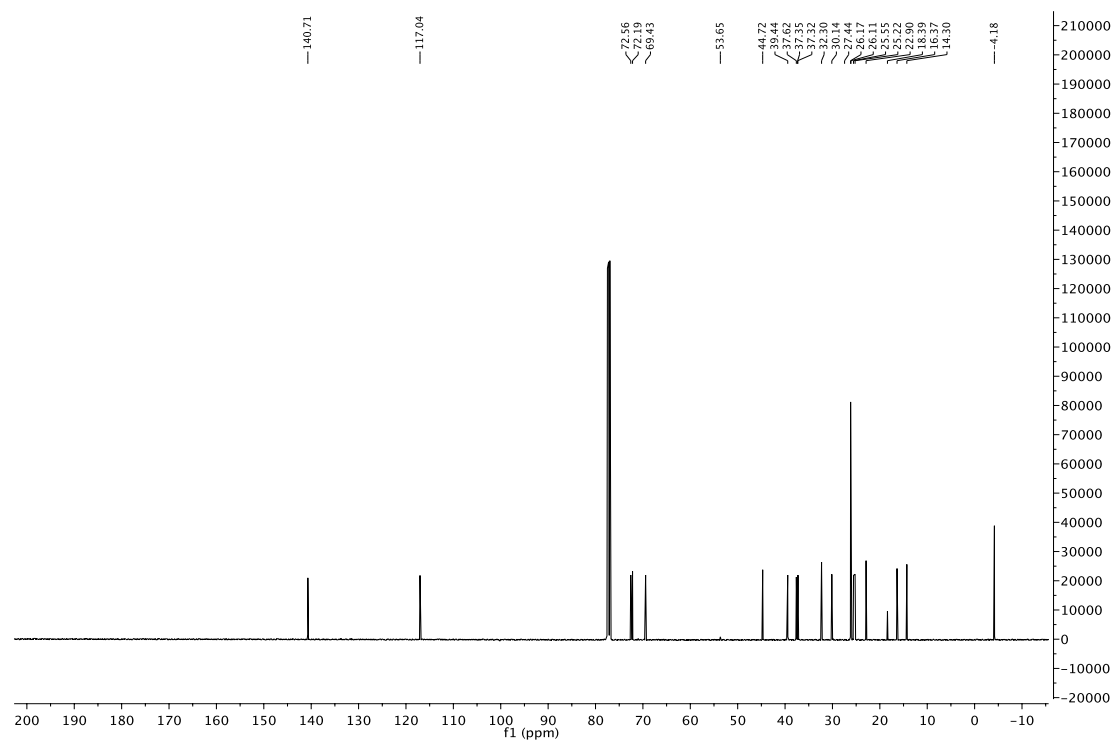
Chemical structure of **3.10.5** is shown above the spectrum. The structure is a bicyclic molecule with a C_5H_{11} group, a TBS group, and two hydroxyl groups.

3.10.5

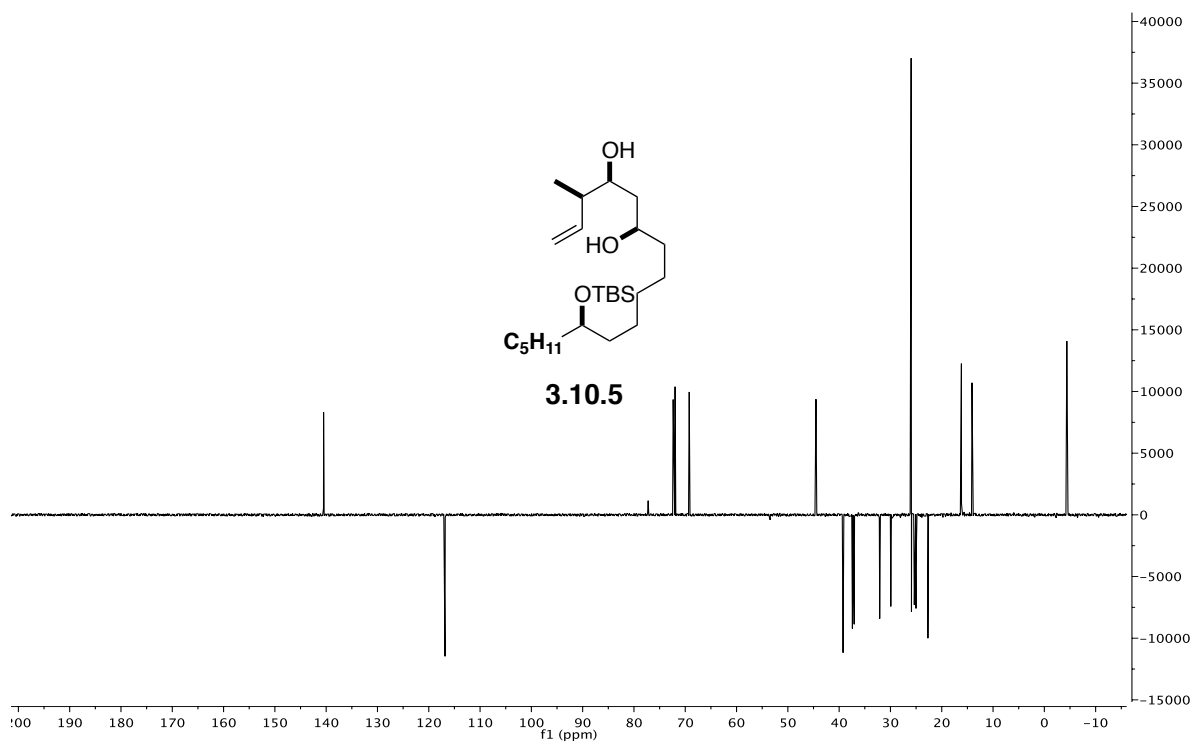
1H NMR spectrum ($CDCl_3$) of compound **3.10.5**. The x-axis represents the chemical shift in ppm (f1), ranging from -0.5 to 9.0. The y-axis represents the intensity, ranging from 0 to 50,000. The spectrum shows several peaks, with integration values provided below the baseline and a list of chemical shifts (δ) on the right side.

Integration values (from left to right): 1.05, 2.09, 1.12, 1.06, 1.00, 2.21, 2.10, 18.01, 3.06, 12.26, 6.00.

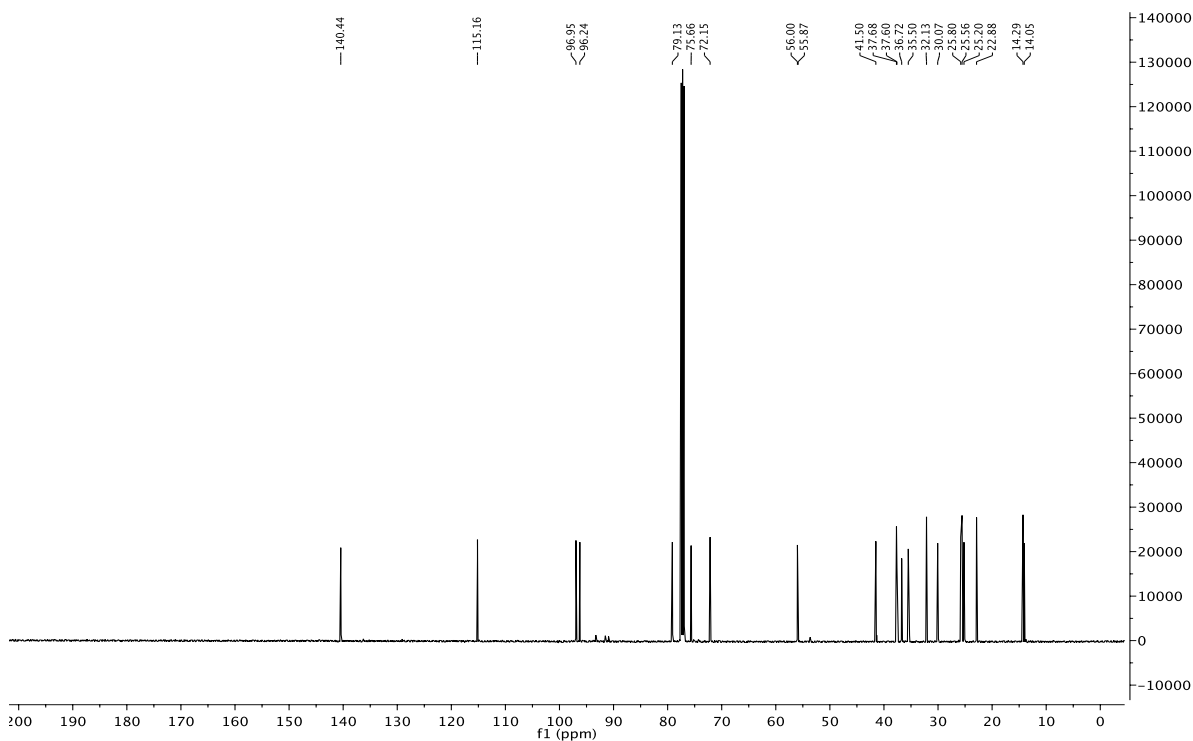
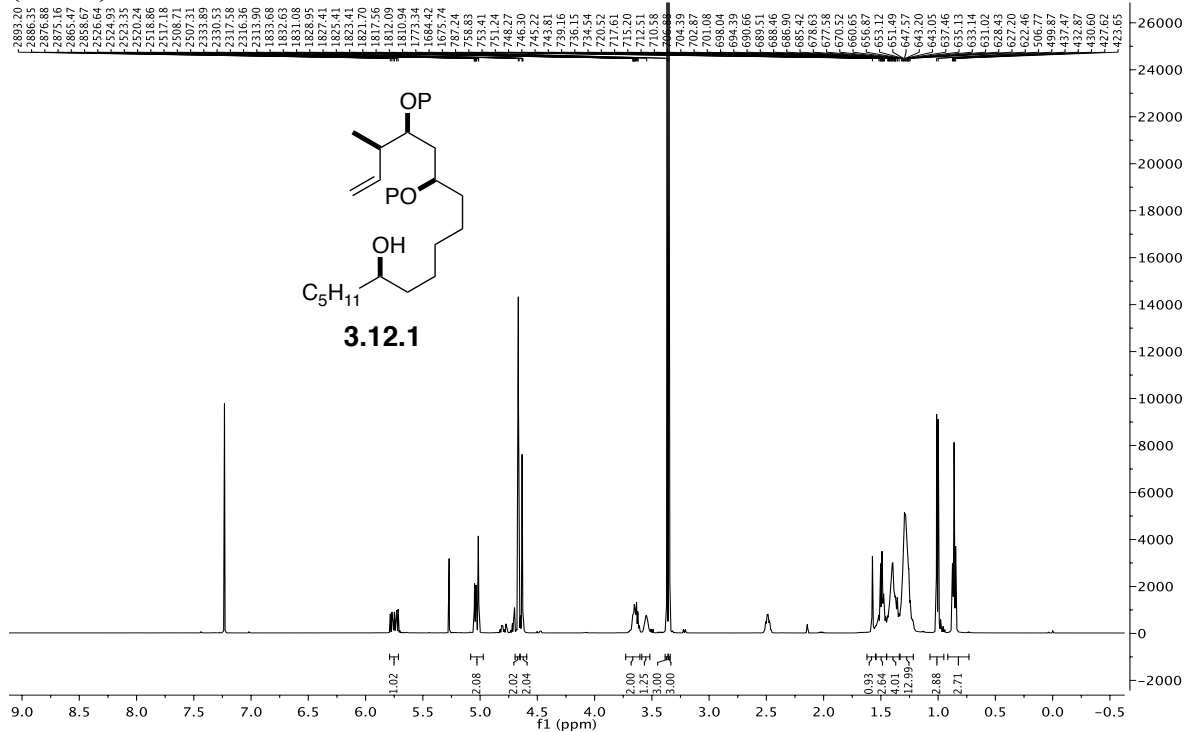
Chemical shifts (δ) (from top to bottom): 5.74, 5.72, 5.70, 5.69, 5.68, 5.67, 5.66, 5.65, 5.64, 5.63, 5.62, 5.61, 5.60, 5.59, 5.58, 5.57, 5.56, 5.55, 5.54, 5.53, 5.52, 5.51, 5.50, 5.49, 5.48, 5.47, 5.46, 5.45, 5.44, 5.43, 5.42, 5.41, 5.40, 5.39, 5.38, 5.37, 5.36, 5.35, 5.34, 5.33, 5.32, 5.31, 5.30, 5.29, 5.28, 5.27, 5.26, 5.25, 5.24, 5.23, 5.22, 5.21, 5.20, 5.19, 5.18, 5.17, 5.16, 5.15, 5.14, 5.13, 5.12, 5.11, 5.10, 5.09, 5.08, 5.07, 5.06, 5.05, 5.04, 5.03, 5.02, 5.01, 5.00, 4.99, 4.98, 4.97, 4.96, 4.95, 4.94, 4.93, 4.92, 4.91, 4.90, 4.89, 4.88, 4.87, 4.86, 4.85, 4.84, 4.83, 4.82, 4.81, 4.80, 4.79, 4.78, 4.77, 4.76, 4.75, 4.74, 4.73, 4.72, 4.71, 4.70, 4.69, 4.68, 4.67, 4.66, 4.65, 4.64, 4.63, 4.62, 4.61, 4.60, 4.59, 4.58, 4.57, 4.56, 4.55, 4.54, 4.53, 4.52, 4.51, 4.50, 4.49, 4.48, 4.47, 4.46, 4.45, 4.44, 4.43, 4.42, 4.41, 4.40, 4.39, 4.38, 4.37, 4.36, 4.35, 4.34, 4.33, 4.32, 4.31, 4.30, 4.29, 4.28, 4.27, 4.26, 4.25, 4.24, 4.23, 4.22, 4.21, 4.20, 4.19, 4.18, 4.17, 4.16, 4.15, 4.14, 4.13, 4.12, 4.11, 4.10, 4.09, 4.08, 4.07, 4.06, 4.05, 4.04, 4.03, 4.02, 4.01, 4.00, 3.99, 3.98, 3.97, 3.96, 3.95, 3.94, 3.93, 3.92, 3.91, 3.90, 3.89, 3.88, 3.87, 3.86, 3.85, 3.84, 3.83, 3.82, 3.81, 3.80, 3.79, 3.78, 3.77, 3.76, 3.75, 3.74, 3.73, 3.72, 3.71, 3.70, 3.69, 3.68, 3.67, 3.66, 3.65, 3.64, 3.63, 3.62, 3.61, 3.60, 3.59, 3.58, 3.57, 3.56, 3.55, 3.54, 3.53, 3.52, 3.51, 3.50, 3.49, 3.48, 3.47, 3.46, 3.45, 3.44, 3.43, 3.42, 3.41, 3.40, 3.39, 3.38, 3.37, 3.36, 3.35, 3.34, 3.33, 3.32, 3.31, 3.30, 3.29, 3.28, 3.27, 3.26, 3.25, 3.24, 3.23, 3.22, 3.21, 3.20, 3.19, 3.18, 3.17, 3.16, 3.15, 3.14, 3.13, 3.12, 3.11, 3.10, 3.09, 3.08, 3.07, 3.06, 3.05, 3.04, 3.03, 3.02, 3.01, 3.00, 2.99, 2.98, 2.97, 2.96, 2.95, 2.94, 2.93, 2.92, 2.91, 2.90, 2.89, 2.88, 2.87, 2.86, 2.85, 2.84, 2.83, 2.82, 2.81, 2.80, 2.79, 2.78, 2.77, 2.76, 2.75, 2.74, 2.73, 2.72, 2.71, 2.70, 2.69, 2.68, 2.67, 2.66, 2.65, 2.64, 2.63, 2.62, 2.61, 2.60, 2.59, 2.58, 2.57, 2.56, 2.55, 2.54, 2.53, 2.52, 2.51, 2.50, 2.49, 2.48, 2.47, 2.46, 2.45, 2.44, 2.43, 2.42, 2.41, 2.40, 2.39, 2.38, 2.37, 2.36, 2.35, 2.34, 2.33, 2.32, 2.31, 2.30, 2.29, 2.28, 2.27, 2.26, 2.25, 2.24, 2.23, 2.22, 2.21, 2.20, 2.19, 2.18, 2.17, 2.16, 2.15, 2.14, 2.13, 2.12, 2.11, 2.10, 2.09, 2.08, 2.07, 2.06, 2.05, 2.04, 2.03, 2.02, 2.01, 2.00, 1.99, 1.98, 1.97, 1.96, 1.95, 1.94, 1.93, 1.92, 1.91, 1.90, 1.89, 1.88, 1.87, 1.86, 1.85, 1.84, 1.83, 1.82, 1.81, 1.80, 1.79, 1.78, 1.77, 1.76, 1.75, 1.74, 1.73, 1.72, 1.71, 1.70, 1.69, 1.68, 1.67, 1.66, 1.65, 1.64, 1.63, 1.62, 1.61, 1.60, 1.59, 1.58, 1.57, 1.56, 1.55, 1.54, 1.53, 1.52, 1.51, 1.50, 1.49, 1.48, 1.47, 1.46, 1.45, 1.44, 1.43, 1.42, 1.41, 1.40, 1.39, 1.38, 1.37, 1.36, 1.35, 1.34, 1.33, 1.32, 1.31, 1.30, 1.29, 1.28, 1.27, 1.26, 1.25, 1.24, 1.23, 1.22, 1.21, 1.20, 1.19, 1.18, 1.17, 1.16, 1.15, 1.14, 1.13, 1.12, 1.11, 1.10, 1.09, 1.08, 1.07, 1.06, 1.05, 1.04, 1.03, 1.02, 1.01, 1.00, 0.99, 0.98, 0.97, 0.96, 0.95, 0.94, 0.93, 0.92, 0.91, 0.90, 0.89, 0.88, 0.87, 0.86, 0.85, 0.84, 0.83, 0.82, 0.81, 0.80, 0.79, 0.78, 0.77, 0.76, 0.75, 0.74, 0.73, 0.72, 0.71, 0.70, 0.69, 0.68, 0.67, 0.66, 0.65, 0.64, 0.63, 0.62, 0.61, 0.60, 0.59, 0.58, 0.57, 0.56, 0.55, 0.54, 0.53, 0.52, 0.51, 0.50, 0.49, 0.48, 0.47, 0.46, 0.45, 0.44, 0.43, 0.42, 0.41, 0.40, 0.39, 0.38, 0.37, 0.36, 0.35, 0.34, 0.33, 0.32, 0.31, 0.30, 0.29, 0.28, 0.27, 0.26, 0.25, 0.24, 0.23, 0.22, 0.21, 0.20, 0.19, 0.18, 0.17, 0.16, 0.15, 0.14, 0.13, 0.12, 0.11, 0.10, 0.09, 0.08, 0.07, 0.06, 0.05, 0.04, 0.03, 0.02, 0.01, 0.00.



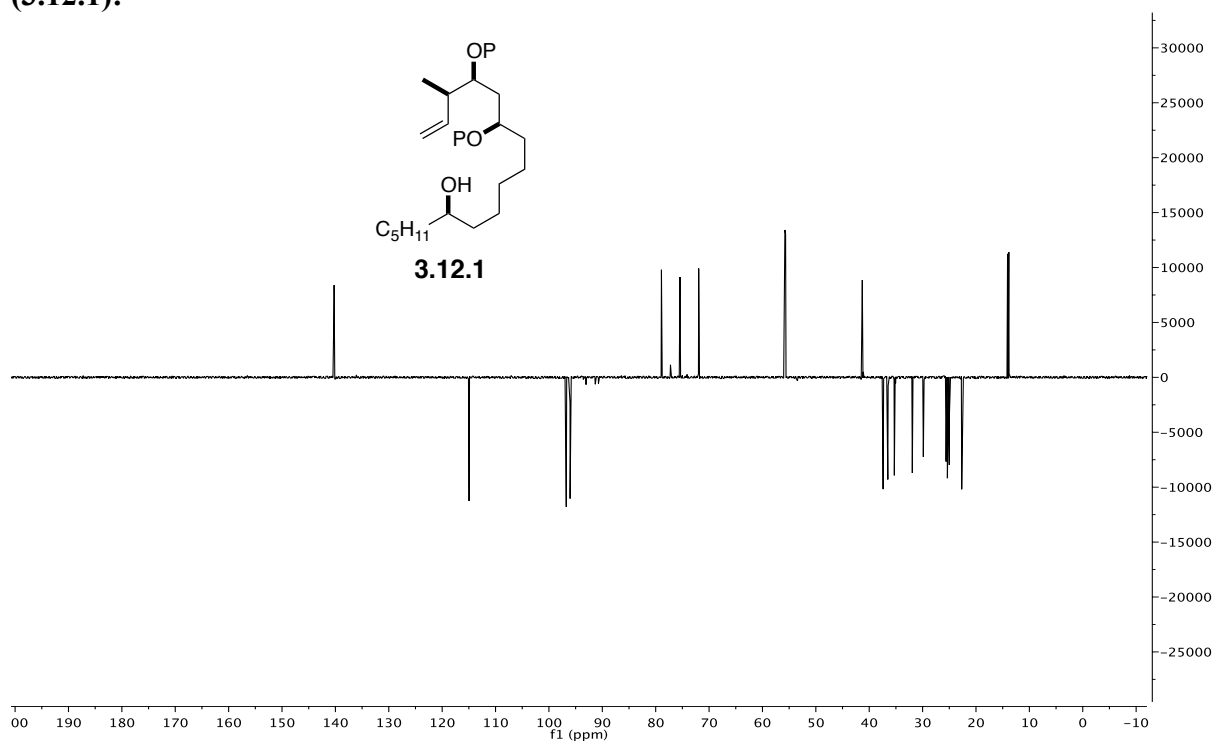
(3*R*,4*S*,6*R*,12*R*)-12-((*tert*-butyldimethylsilyl)oxy)-3-methylheptadec-1-ene-4,6-diol
(3.10.5):



**(6*R*,12*R*,14*S*,15*R*)-12,14-bis(methoxymethoxy)-15-methylheptadec-16-en-6-ol
(3.12.1):**



**(6*R*,12*R*,14*S*,15*R*)-12,14-bis(methoxymethoxy)-15-methylheptadec-16-en-6-ol
(3.12.1):**



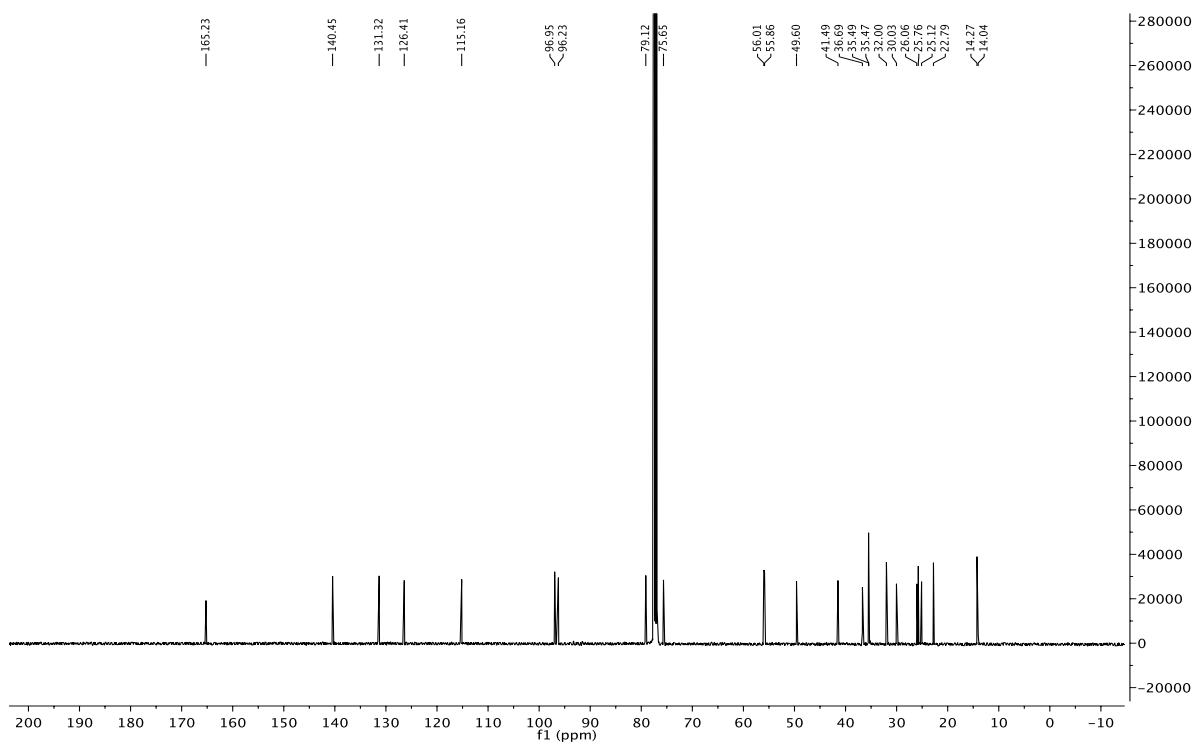
3.11.3

P = MOM

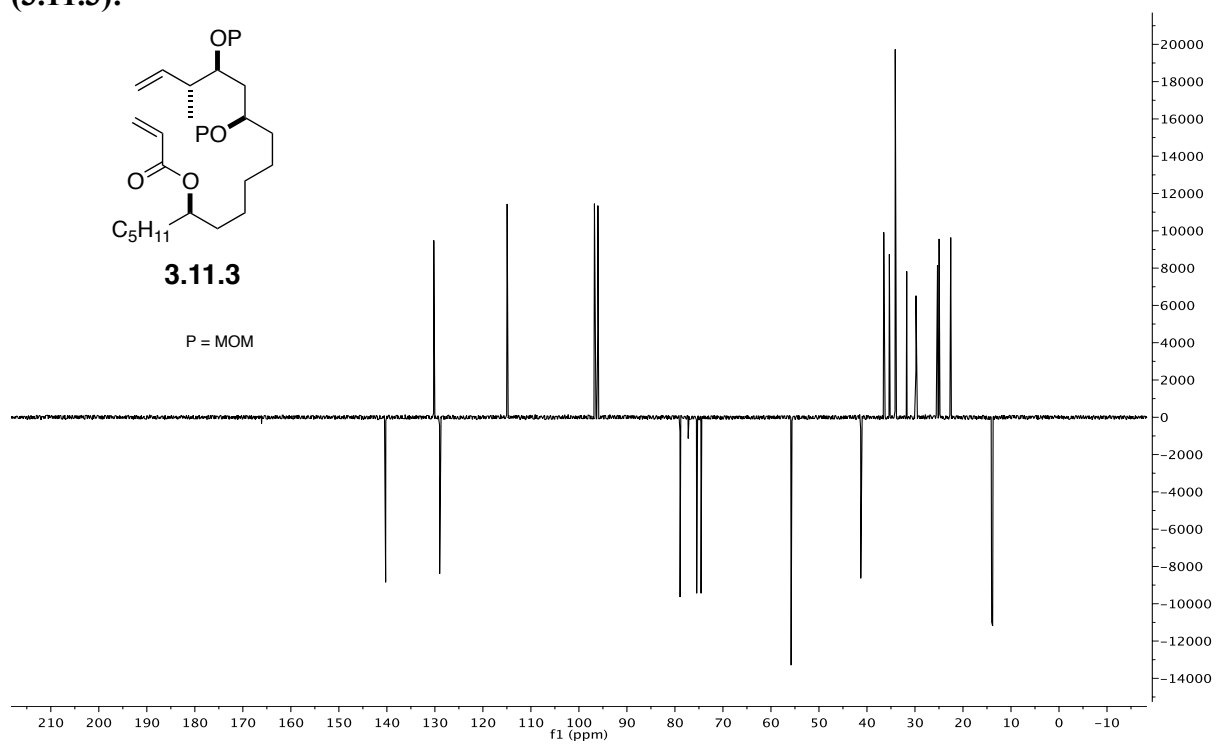
CCCCCOC1(COP(=O)(OC)COP(=O)(OC)C1)C=C

¹H NMR spectrum (CDCl₃) of compound **3.11.3**. The x-axis represents the chemical shift in ppm (f1), ranging from -0.5 to 9.0. The y-axis represents the intensity, ranging from 0 to 40,000. The spectrum shows several peaks, with integration values provided below the baseline. The chemical structure of **3.11.3** is shown above the spectrum, indicating it is a phosphonate derivative (P = MOM).

Chemical Shift (ppm)	Integration
~7.2	1.00
~6.2	0.99
~5.8	2.07
~5.0	2.08
~4.8	1.11
~4.6	1.99
~4.4	1.98
~3.6	2.04
~3.4	3.01
~3.2	3.01
~2.6	0.67
~1.6	7.22
~1.4	13.75
~1.2	3.00
~1.0	3.08



**(3*R*,4*S*,6*R*,12*R*)-12-((*tert*-butyldimethylsilyl)oxy)-3-methylheptadec-1-ene-4,6-diol
(3.11.3):**



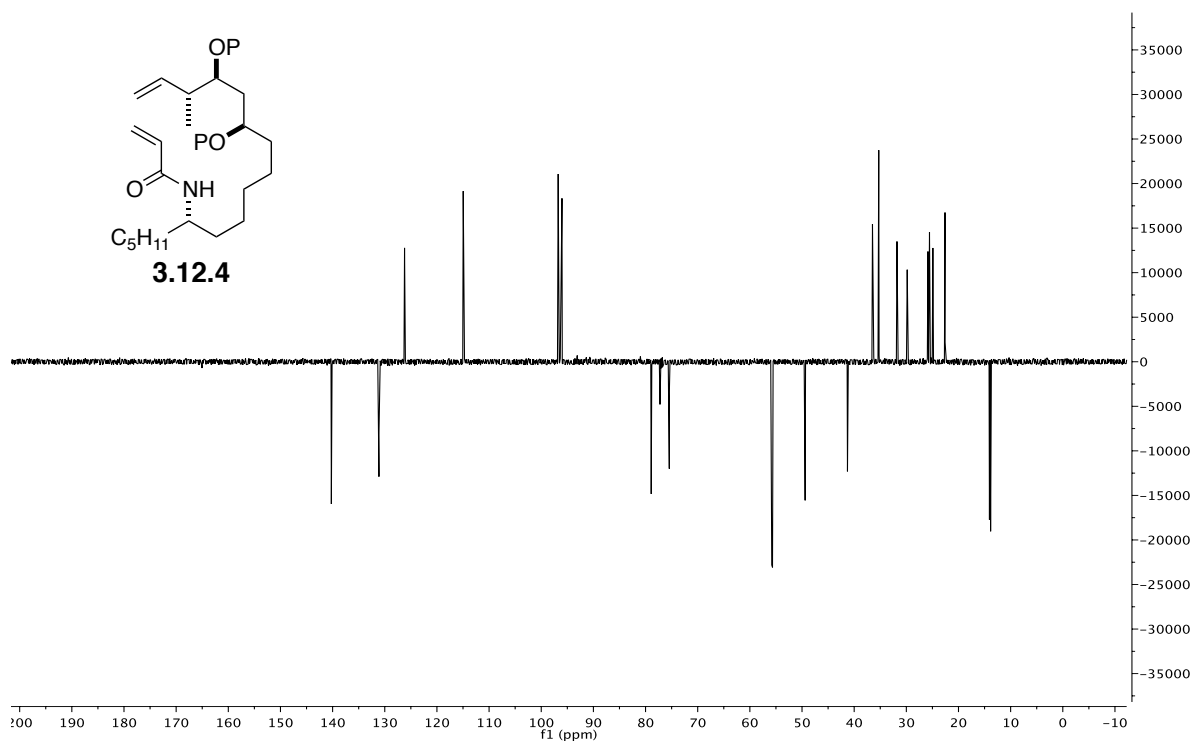
Chemical structure of **3.12.4** is shown above the spectrum. The structure is a complex molecule featuring a long chain with a terminal C_5H_{11} group, a carbonyl group ($C=O$), and a nitrogen atom (NH). The chain also contains several double bonds and a terminal OP group.

The 1H NMR spectrum (CDCl₃) shows the following chemical shifts (ppm) and integrations:

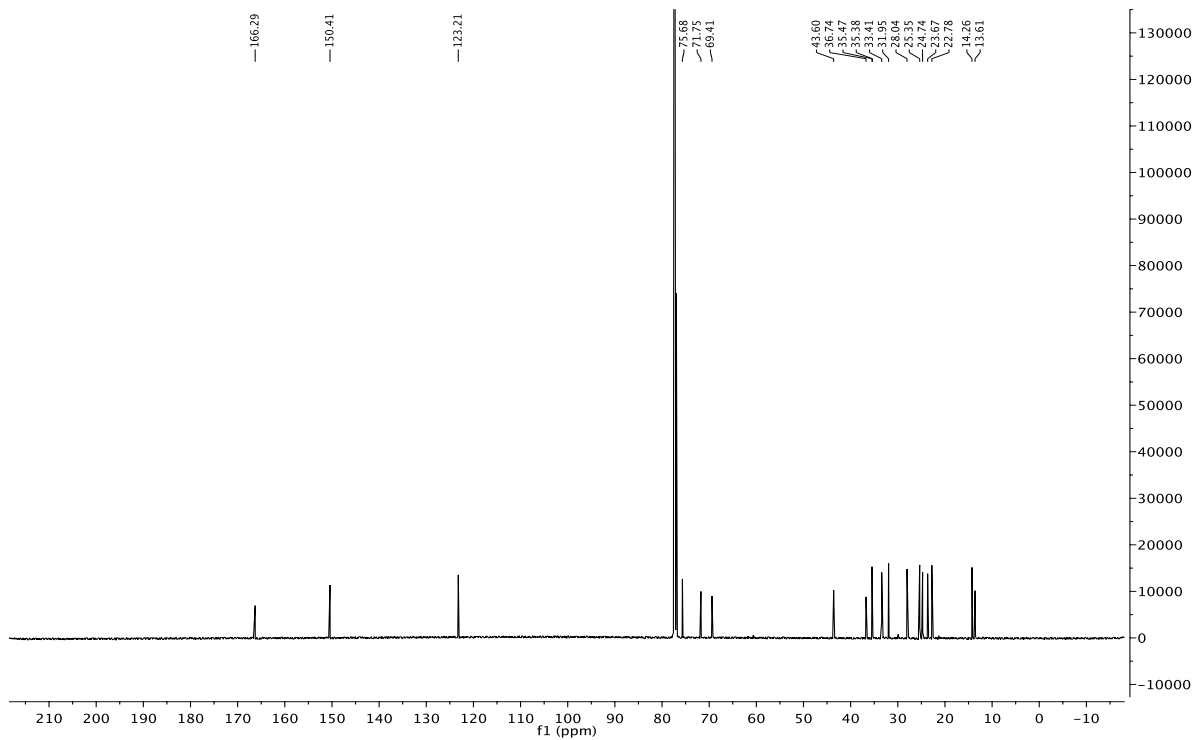
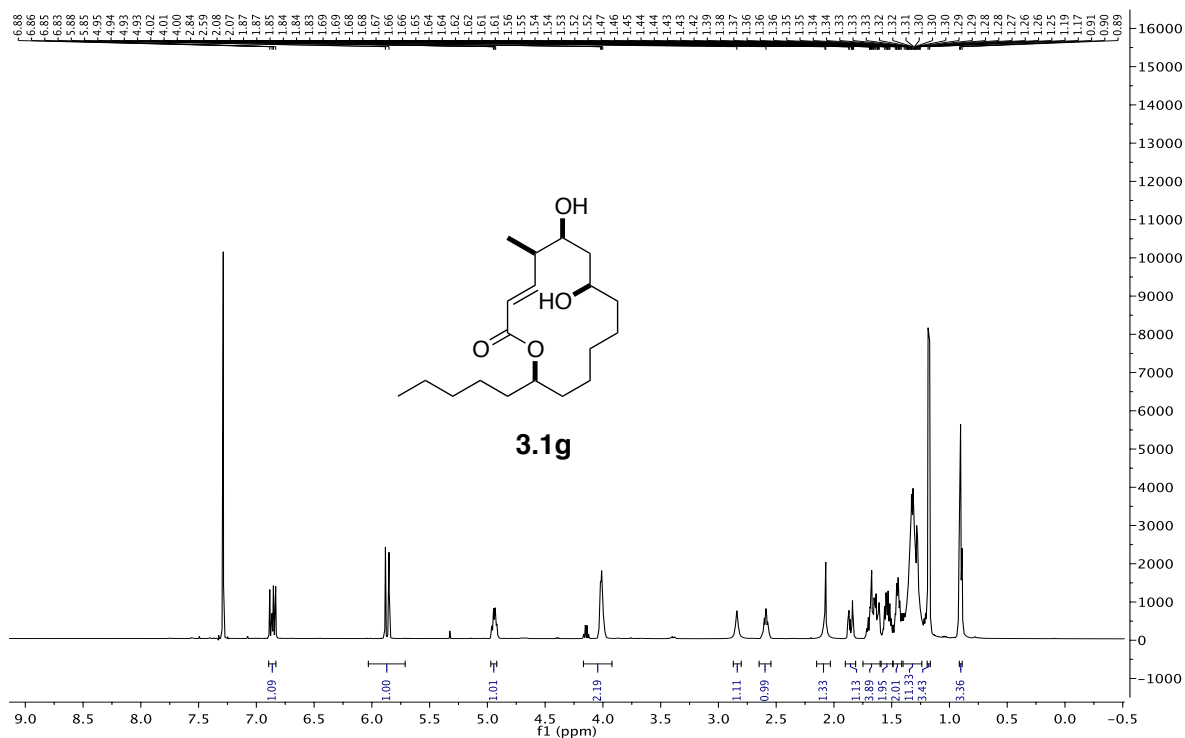
- ~7.2 ppm (integration 1.06)
- ~6.2 ppm (integration 1.01)
- ~5.8 ppm (integration 1.06)
- ~5.5 ppm (integration 1.11)
- ~5.2 ppm (integration 1.11)
- ~4.8 ppm (integration 1.04)
- ~4.5 ppm (integration 1.92)
- ~4.2 ppm (integration 2.15)
- ~4.0 ppm (integration 1.10)
- ~3.8 ppm (integration 2.14)
- ~3.5 ppm (integration 3.07)
- ~3.2 ppm (integration 2.99)
- ~2.5 ppm (integration 0.87)
- ~1.8 ppm (integration 3.84)
- ~1.5 ppm (integration 17.24)
- ~1.2 ppm (integration 3.15)
- ~1.0 ppm (integration 3.30)



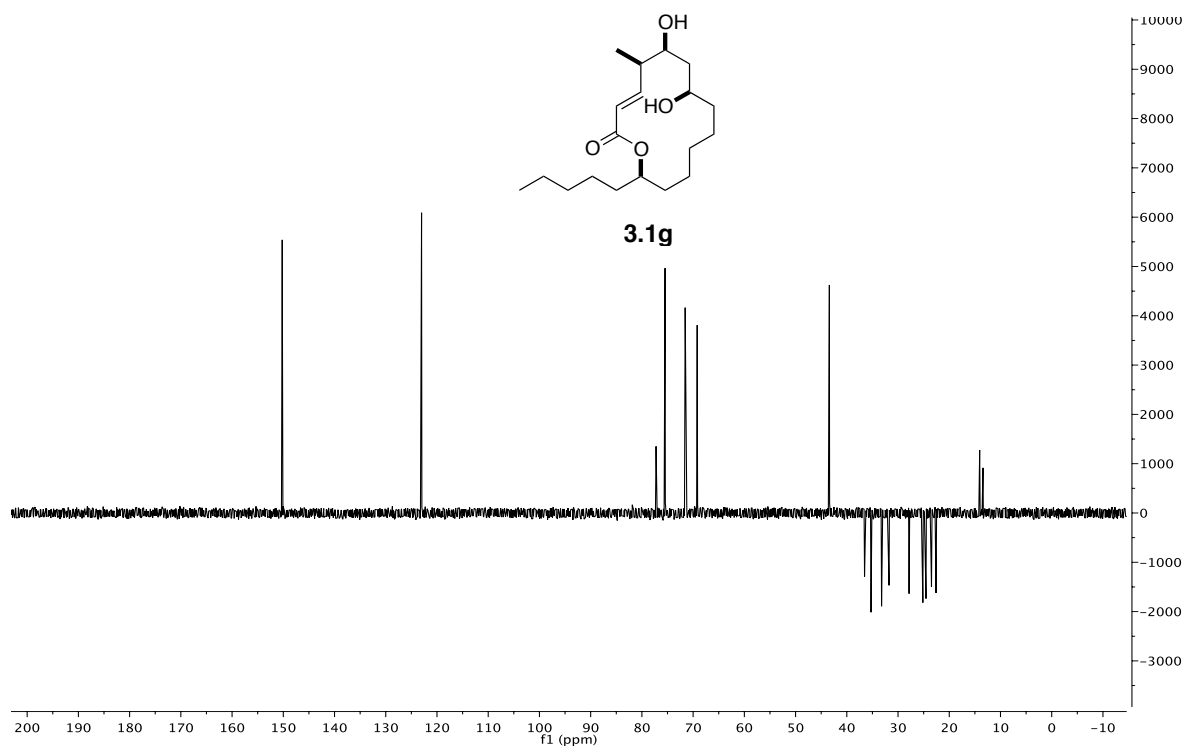
di-*tert*-butyl ((3*R*,4*R*,6*S*,12*S*)-12-acrylamido-3-methylheptadec-1-ene-4,6-diyl) dicar-
bamate (3.12.4):



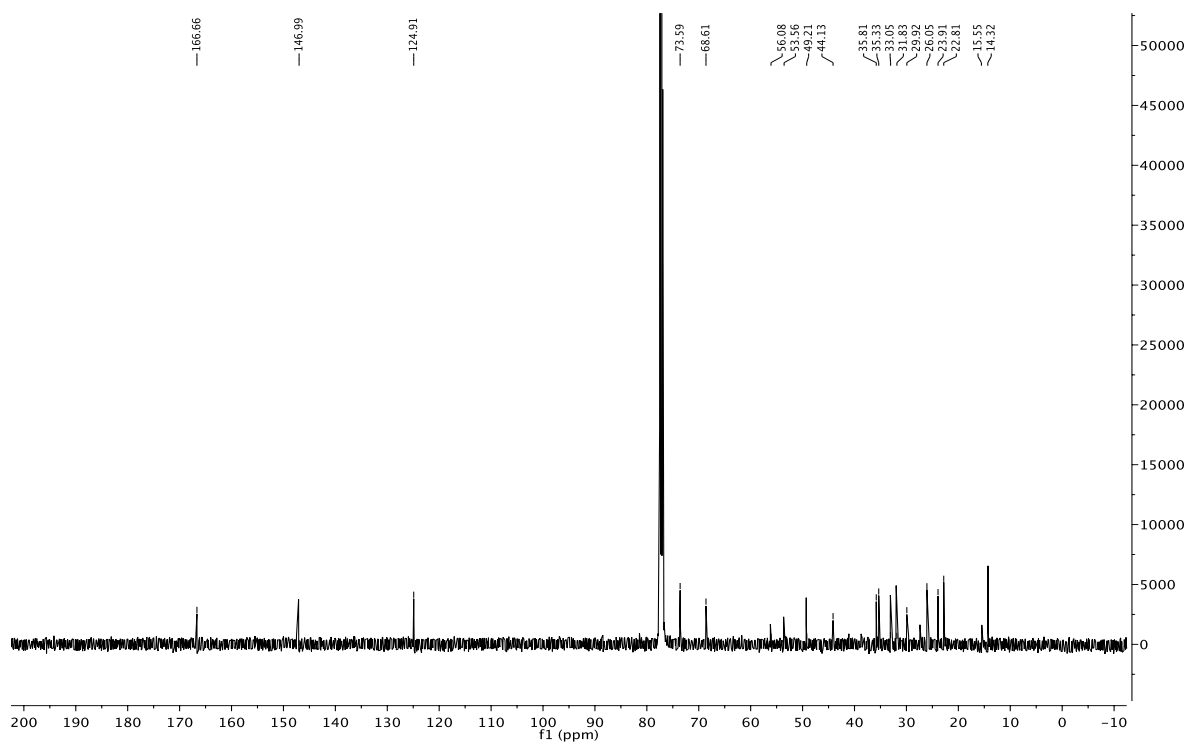
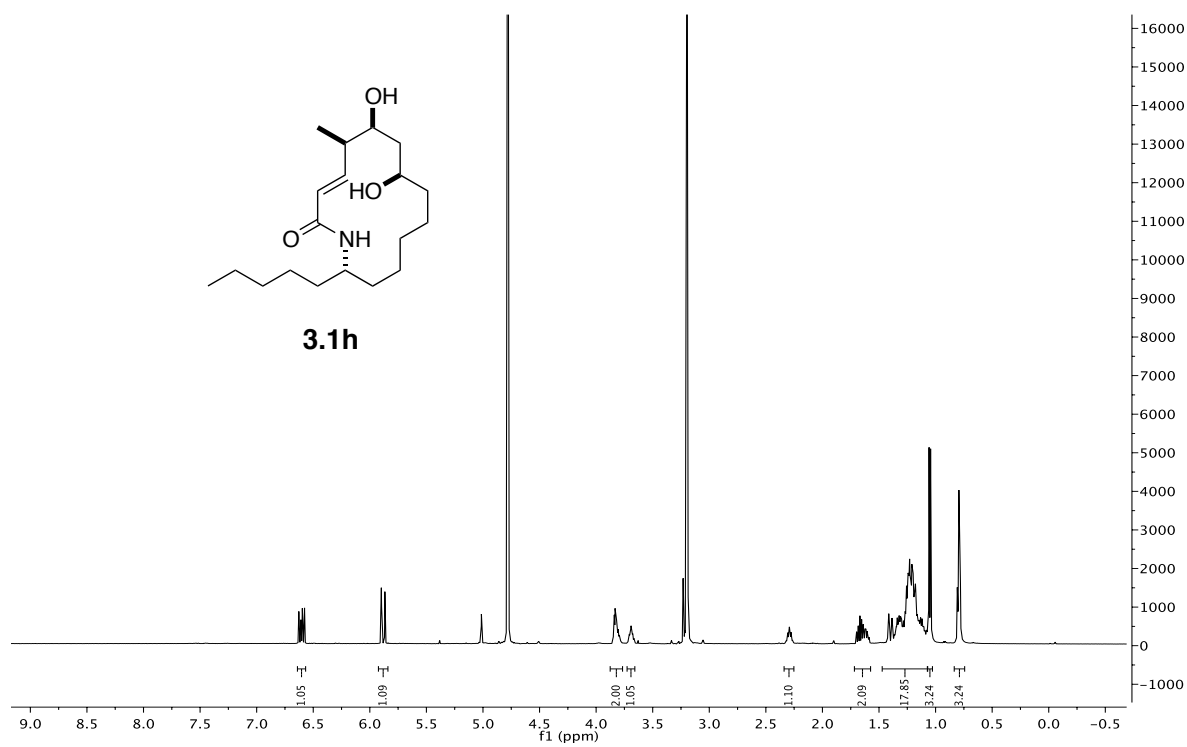
**(5*R*,6*S*,8*R*,14*R*,*E*)-6,8-dihydroxy-5-methyl-14-pentylloxacyclotetradec-3-en-2-one
(3.1g):**



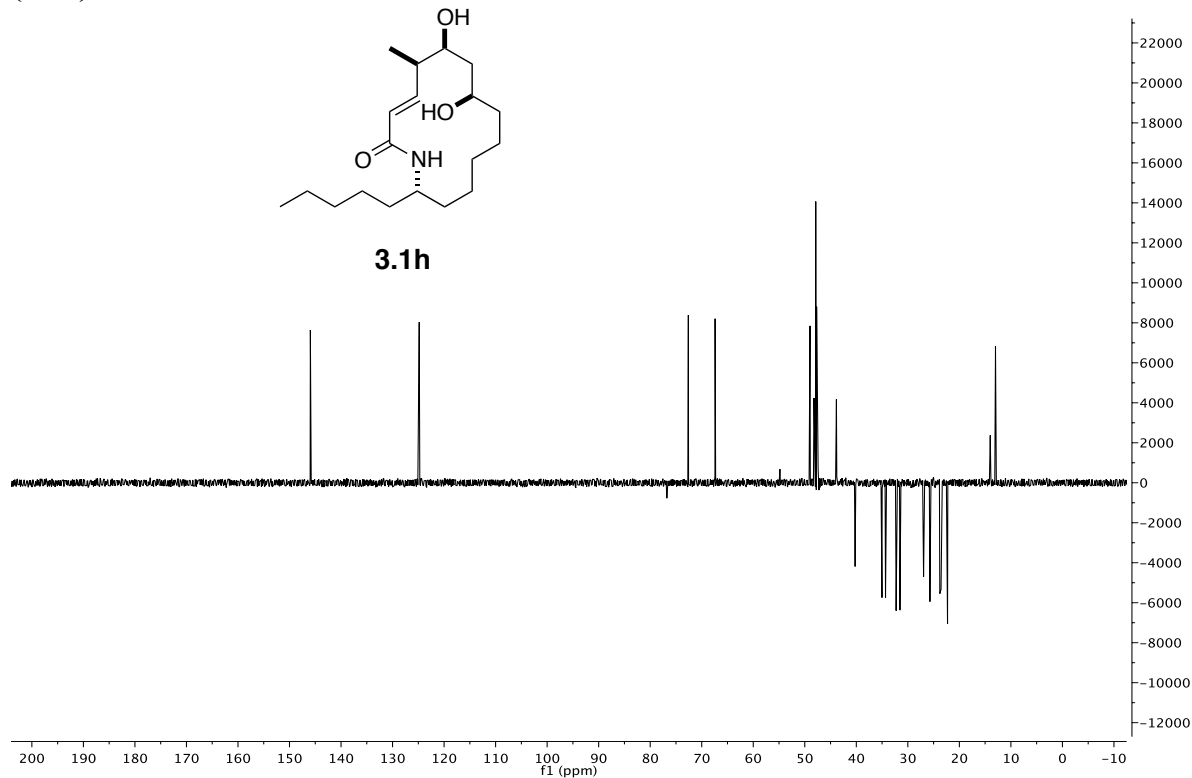
**(5*R*,6*S*,8*R*,14*R*,*E*)-6,8-dihydroxy-5-methyl-14-pentyloxacyclotetradec-3-en-2-one
(3.1g):**



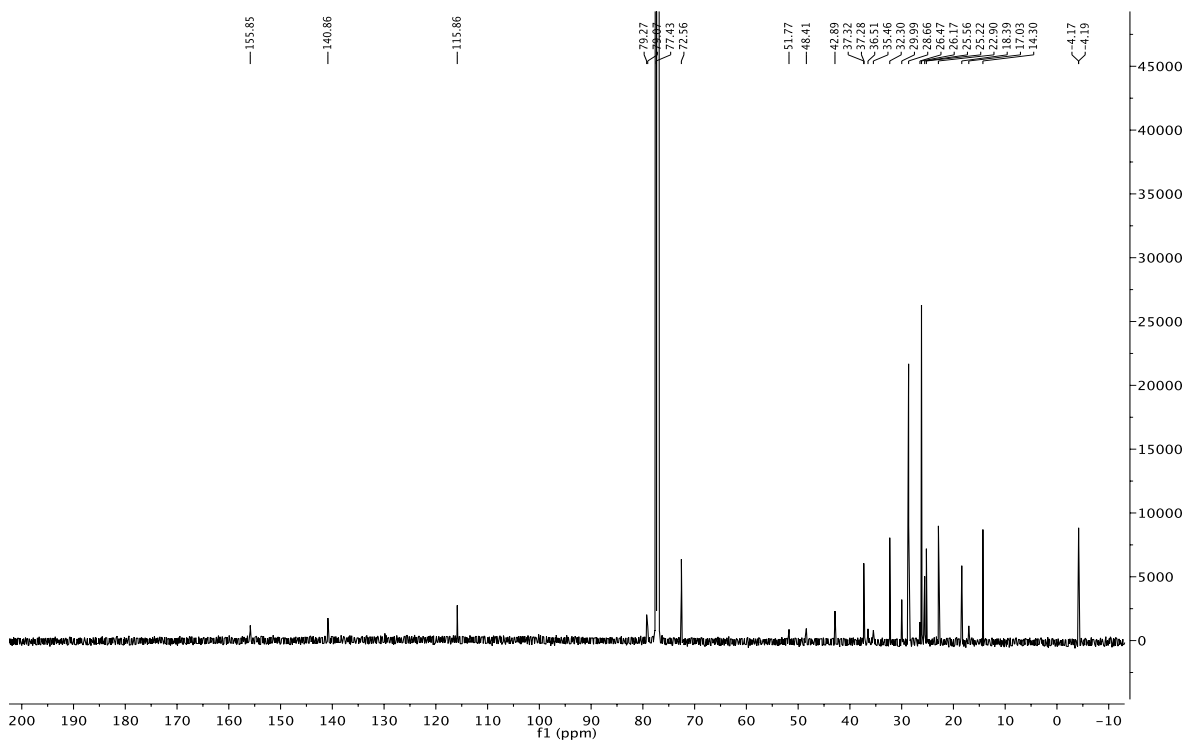
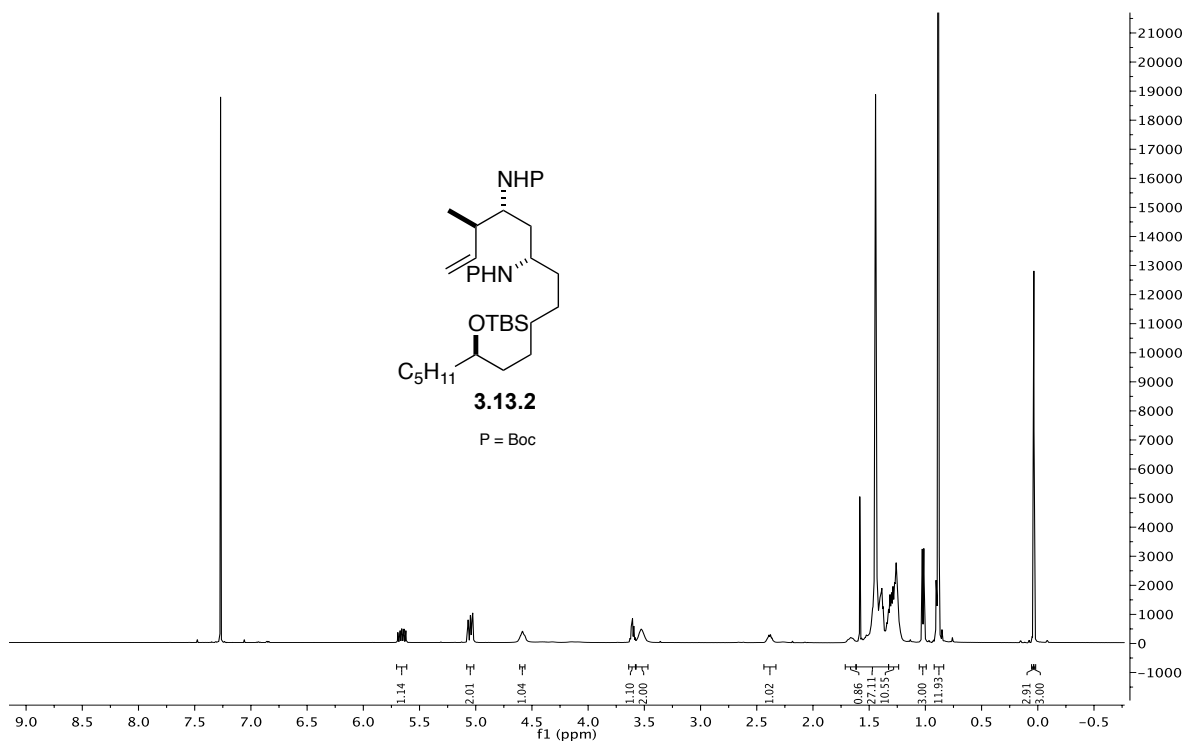
**(5*R*,6*S*,8*R*,14*S*,*E*)-6,8-dihydroxy-5-methyl-14-pentylazacyclotetradec-3-en-2-one
(3.1h):**



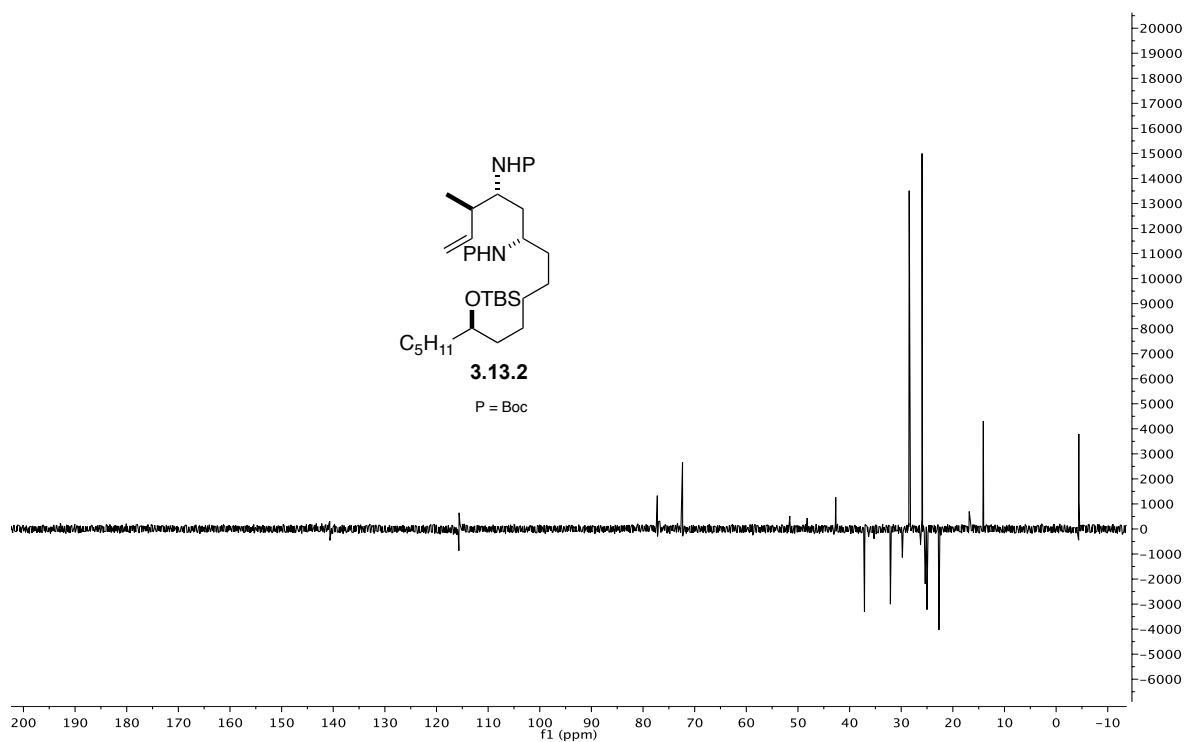
**(5*R*,6*S*,8*R*,14*S*,*E*)-6,8-dihydroxy-5-methyl-14-pentylazacyclotetradec-3-en-2-one
(3.1h):**



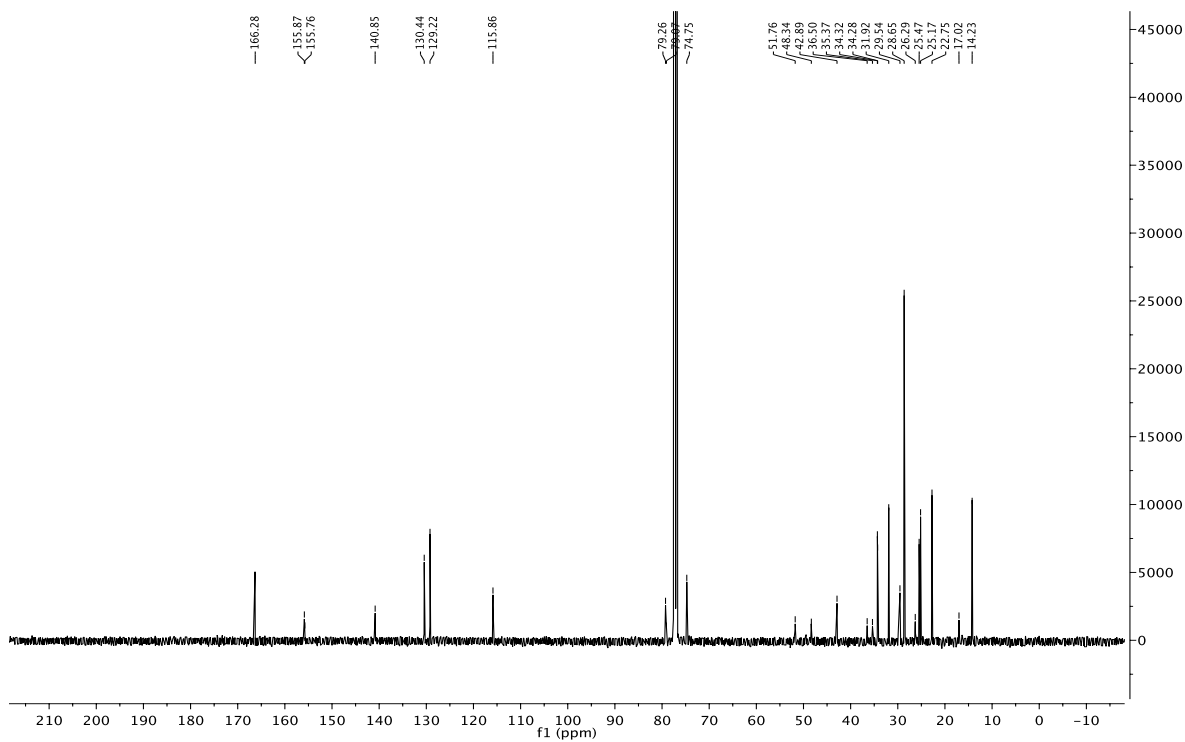
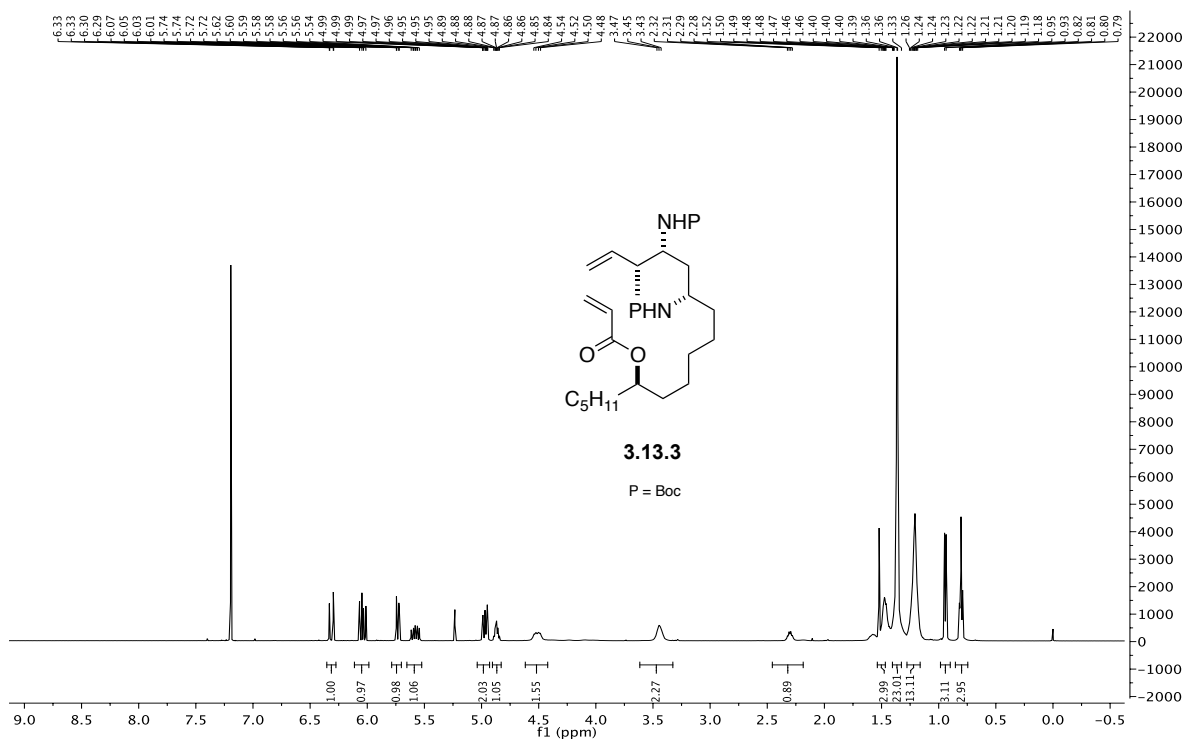
di-*tert*-butyl ((3*R*,4*R*,6*S*,12*R*)-12-((*tert*-butyldimethylsilyl)oxy)-3-methylhepta-dec-1-ene-4,6-diyl)dicarbamate (3.13.2):



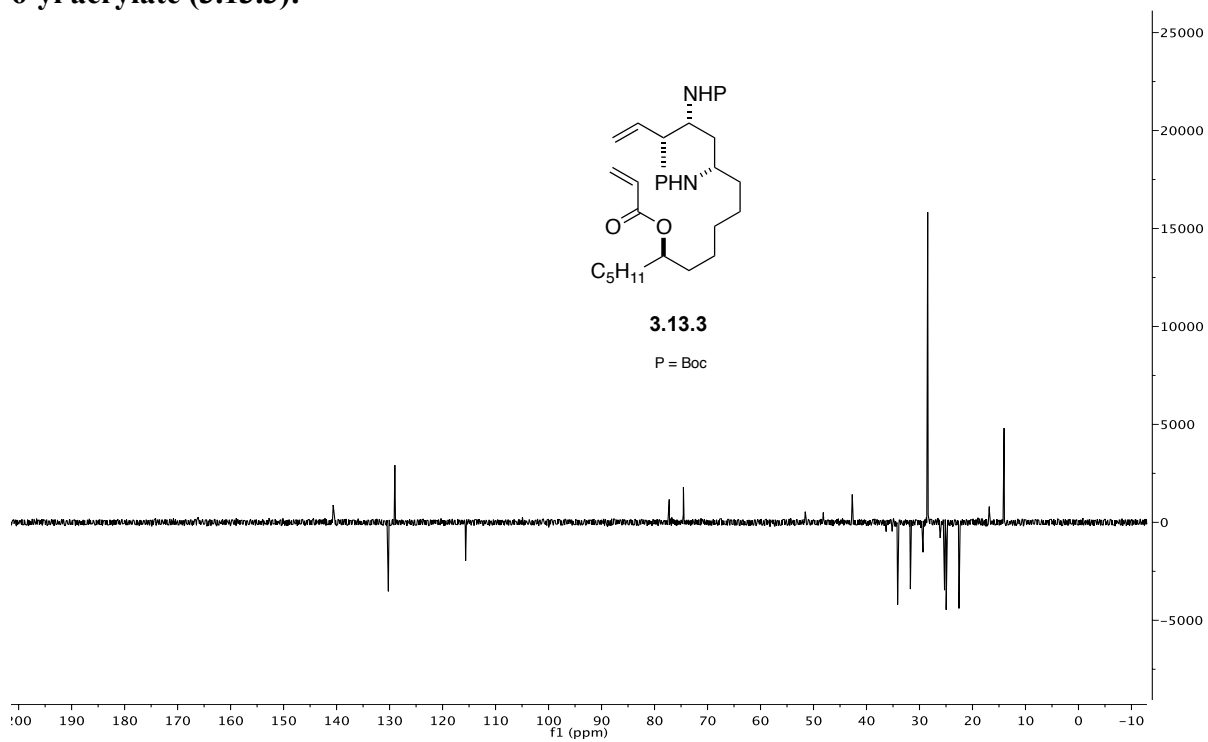
di-*tert*-butyl ((3*R*,4*R*,6*S*,12*R*)-12-((*tert*-butyldimethylsilyl)oxy)-3-methylhepta-dec-1-ene-4,6-diyl)dicarbamate (3.13.2).



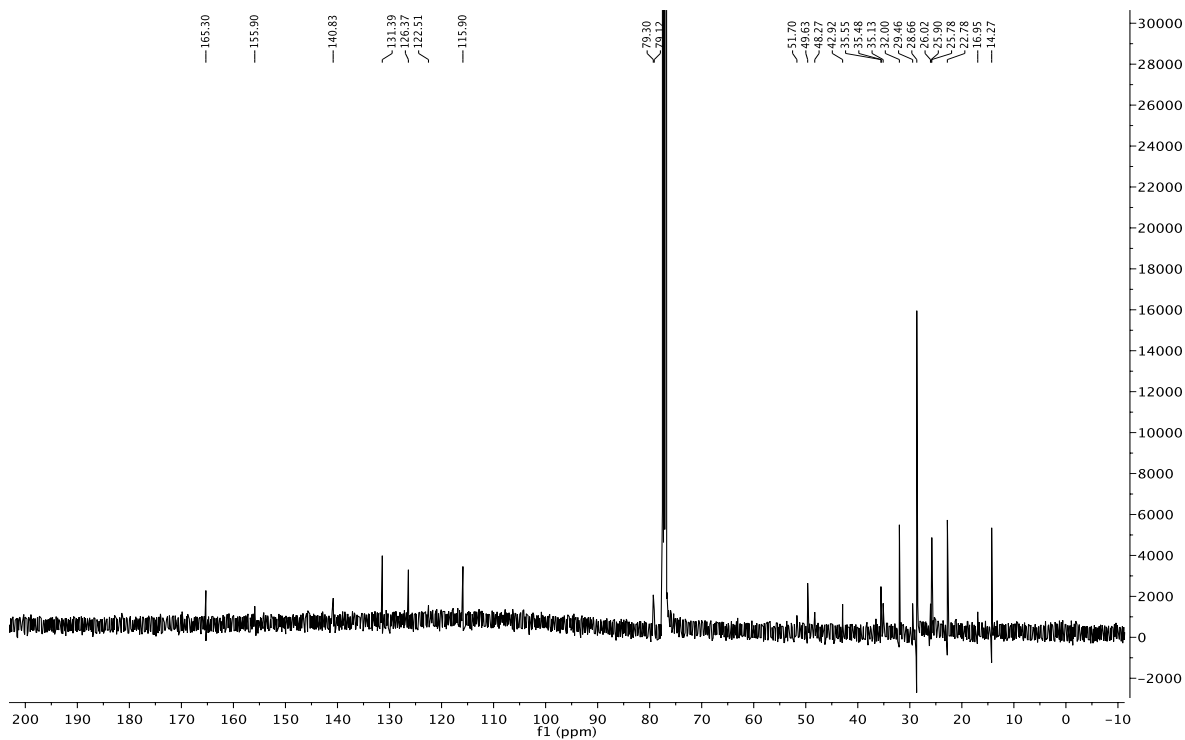
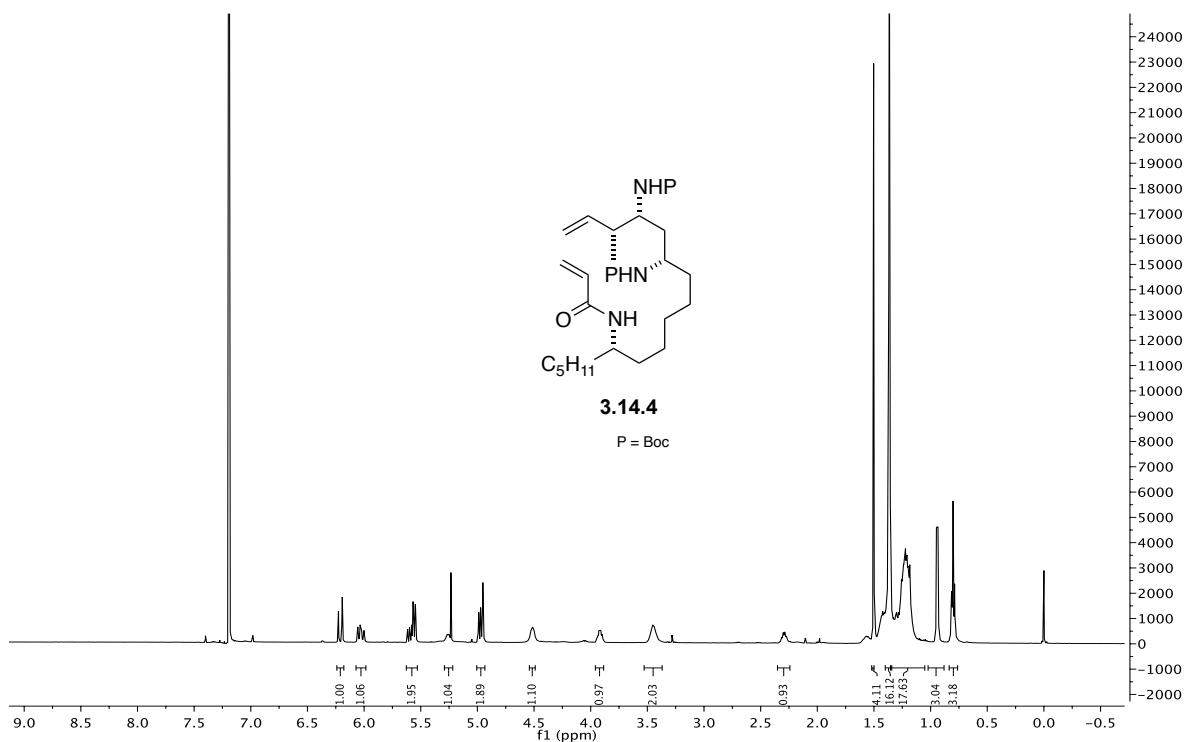
(6*R*,12*S*,14*R*,15*R*)-12,14-bis((*tert*-butoxycarbonyl)amino)-15-methylheptadec-16-en-6-yl acrylate (3.13.3):



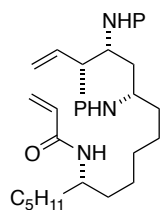
(6*R*,12*S*,14*R*,15*R*)-12,14-bis((*tert*-butoxycarbonyl)amino)-15-methylheptadec-16-en-6-yl acrylate (3.13.3):



di-*tert*-butyl ((3*R*,4*R*,6*S*,12*S*)-12-acrylamido-3-methylheptadec-1-ene-4,6-diyl) dicarbamate (3.14.4):

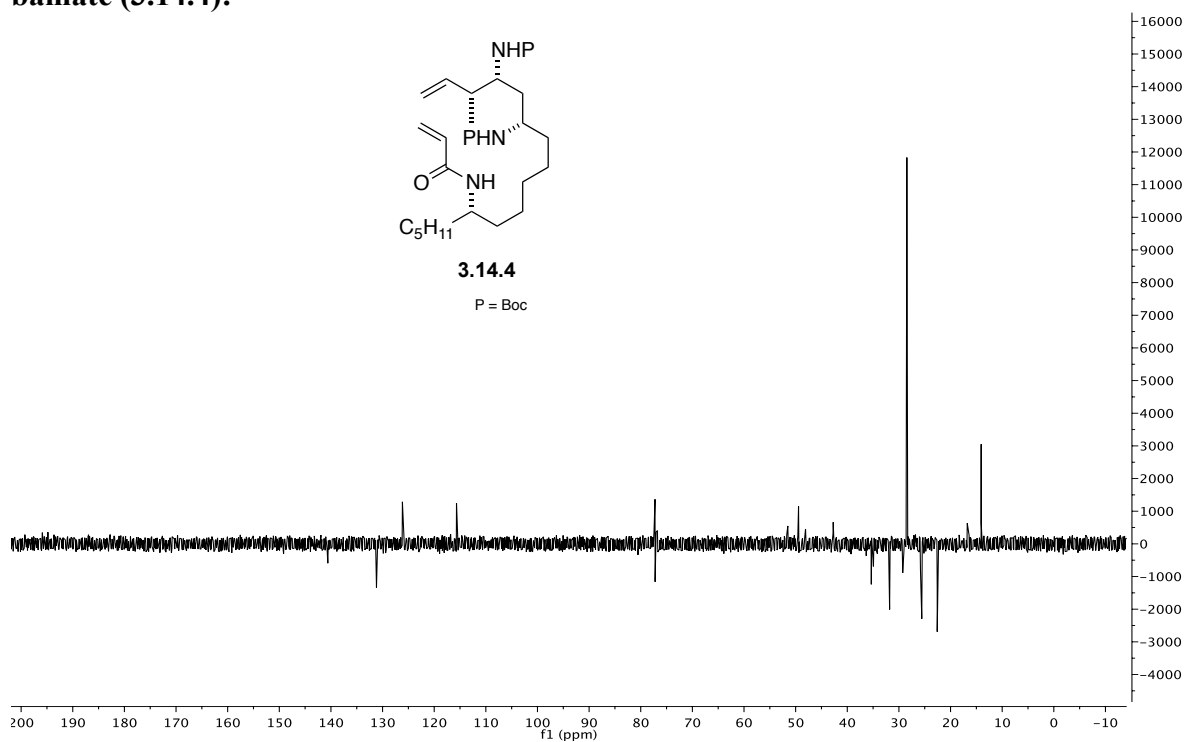


di-*tert*-butyl ((3*R*,4*R*,6*S*,12*S*)-12-acrylamido-3-methylheptadec-1-ene-4,6-diyl) dicarbamate (3.14.4):



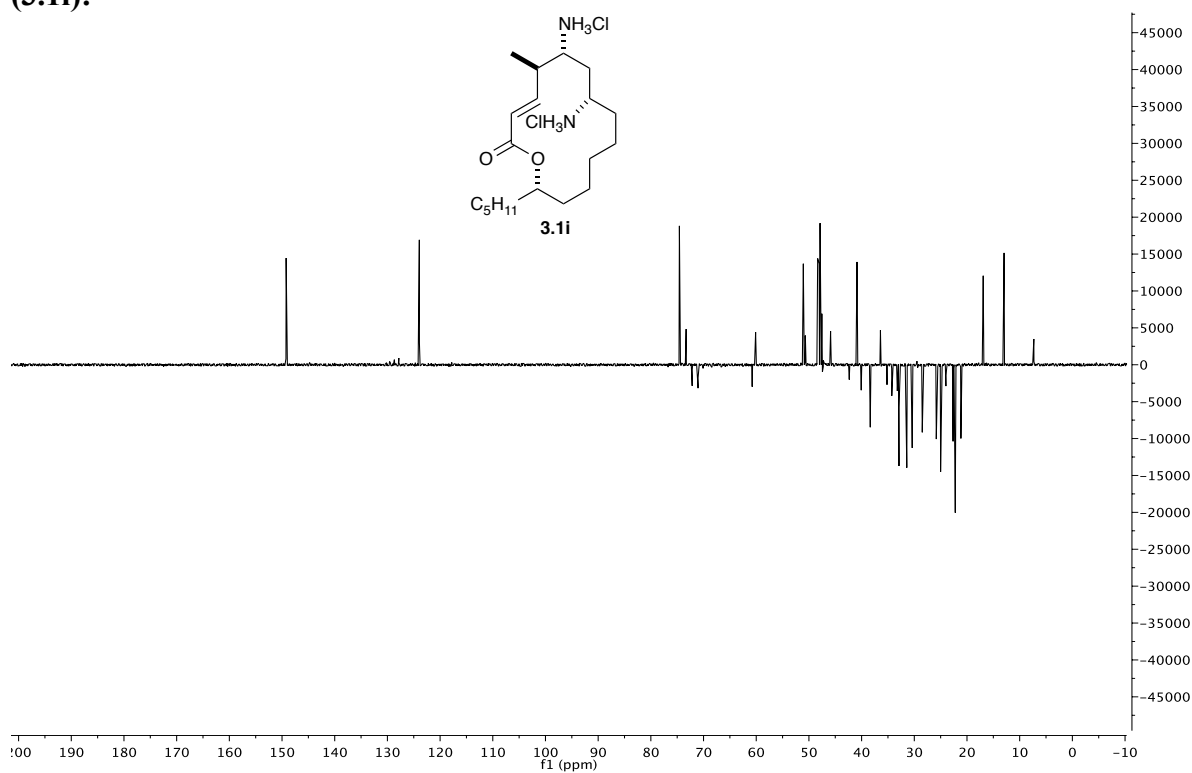
3.14.4

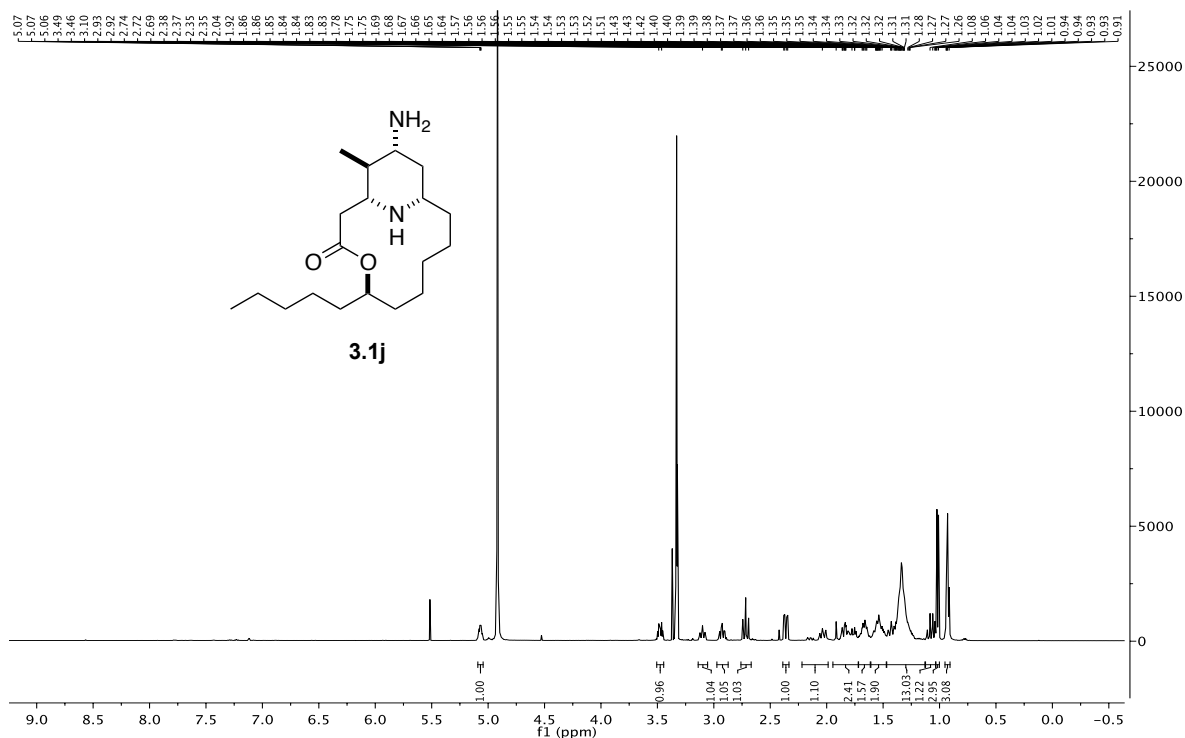
P = Boc



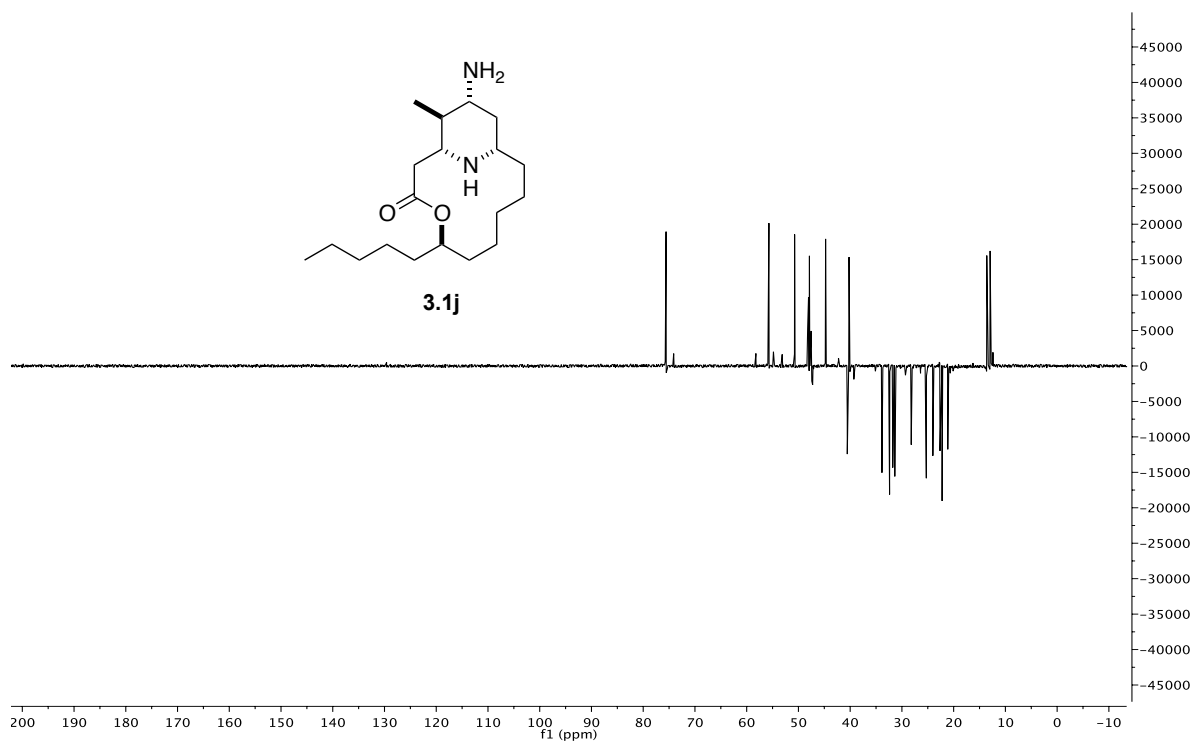


**(5*R*,6*R*,8*S*,14*R*,*E*)-6,8-diamino-5-methyl-14-pentyloxacyclotetradec-3-en-2-one (Salt)
(3.1i):**

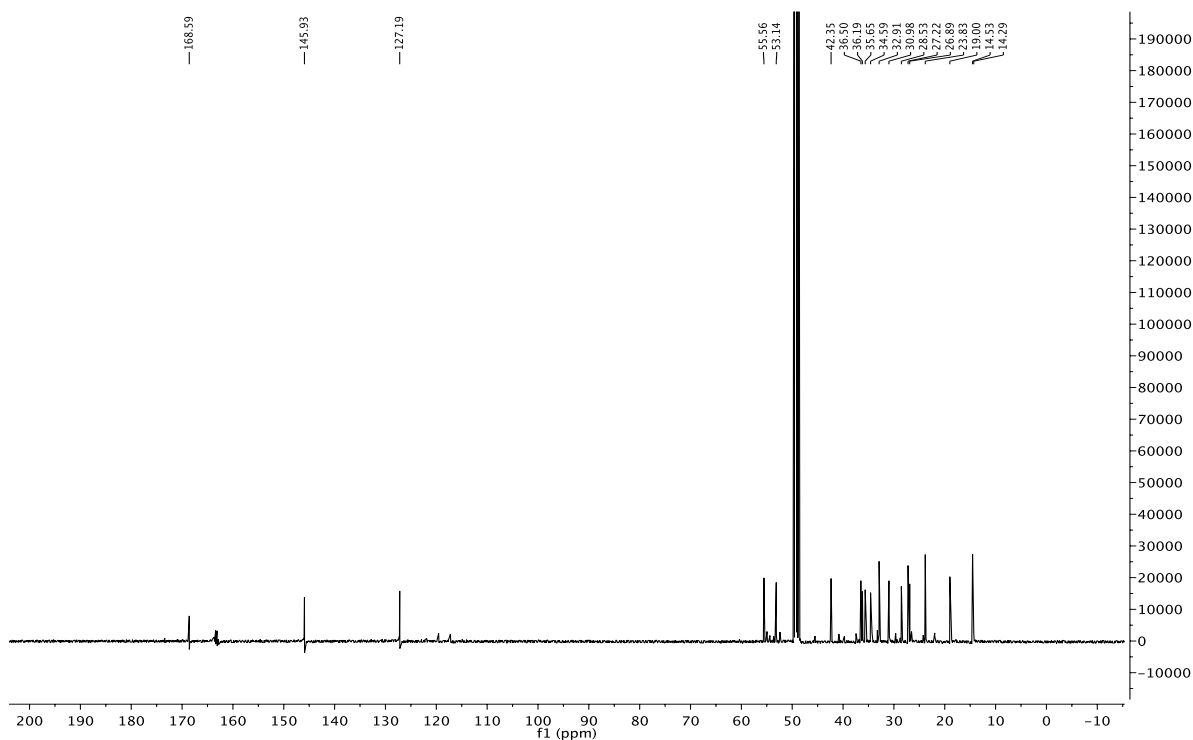
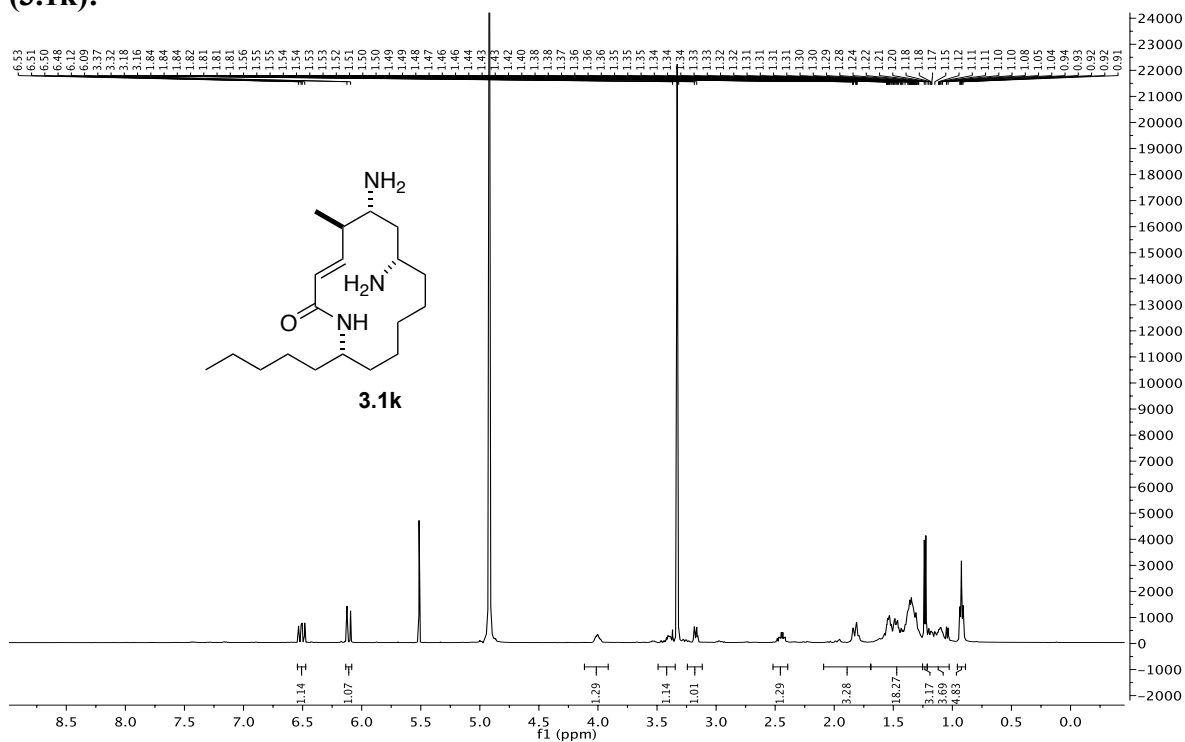




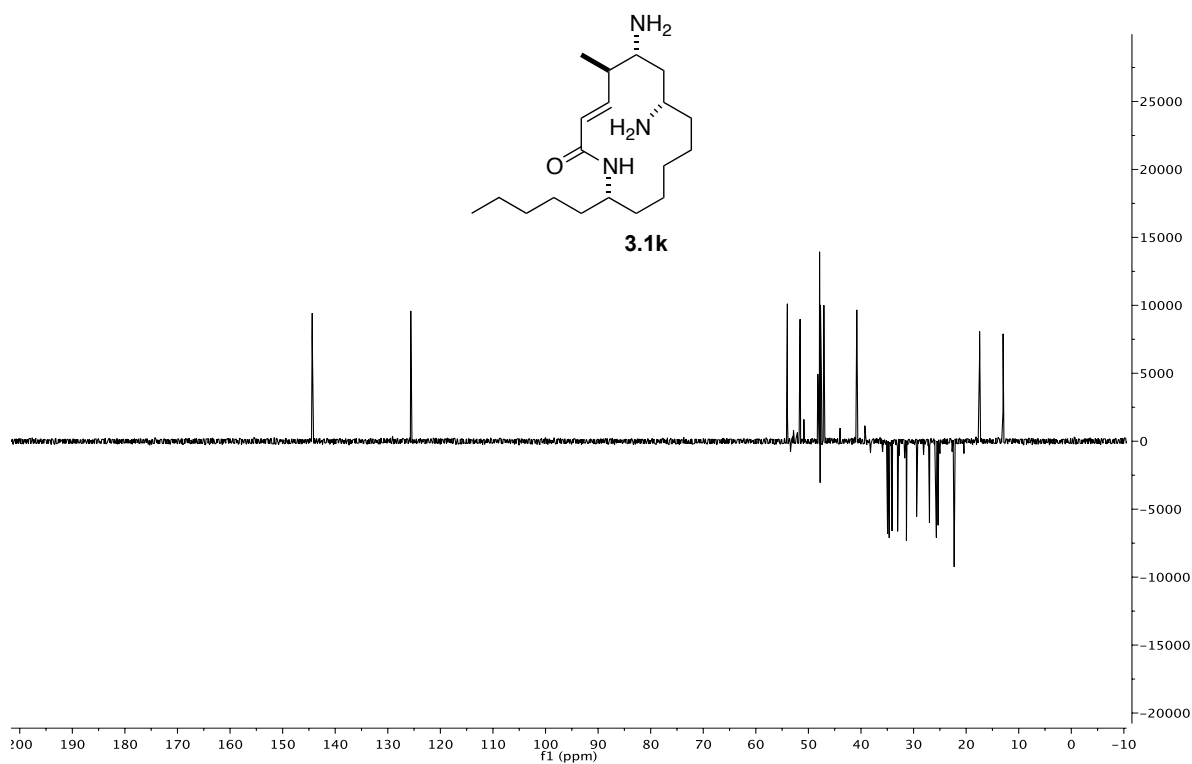
(6*R*,12*S*,14*R*,15*R*)-12,14-bis((*tert*-butoxycarbonyl)amino)-15-methylheptadec-16-en-6-yl acrylate (3.1j):



**(5*R*,6*R*,8*S*,14*S*,*E*)-6,8-diamino-5-methyl-14-pentylazacyclotetradec-3-en-2-one
(3.1k):**

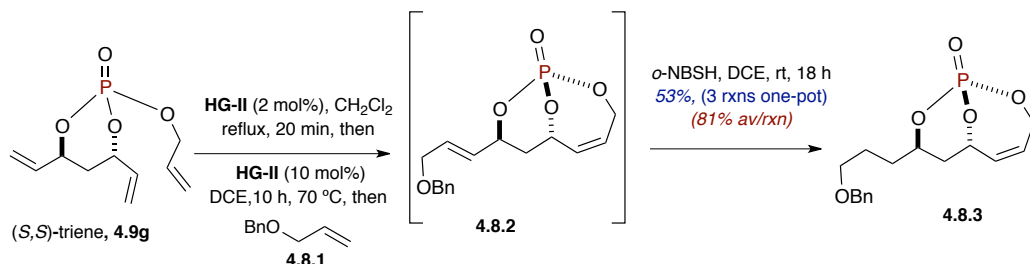


**(5*R*,6*R*,8*S*,14*S*,*E*)-6,8-diamino-5-methyl-14-pentylazacyclotetradec-3-en-2-one
(3.1k):**



5.3: Efforts Towards Asymmetric Total Synthesis of (–)-13-Desmethyl-lyngbouilloside an Unnatural Analog of Lyngbouillosid (Chapter 4)

(1*S*,6*S*,8*R*)-8-(3-(benzyloxy)propyl)-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-ene 1-oxide (4.8.3):



To a solution of (*S,S*)-triene 4.9g (400 mg, 1.7 mmol) in a degassed CH₂Cl₂ (347 mL, 0.005 M) was added **HG-II** (21.2 mg, 0.034 mmol, 2 mol%) the reaction mixture was refluxed for 20 min. After completion of RCM reaction, CH₂Cl₂ was evaporated under reduced pressure. To the crude product was added freshly distilled, freeze-degassed 1,2-dichloroethane (DCE) (17 mL, 0.1 M), the cross metathesis (CM) partner **4.8.1** (327 mg, 2.2 mmol) and **HG-II** (63 mg, 0.06 mmol, 6 mol%) under argon. The reaction mixture was stirred at 70 °C for 5 h and a second portion of **HG-II** (42 mg, 0.068 mmol, 4 mol%) and CM partner (75 mg, 0.51 mmol) were added to the reaction mixture, and was stirred at 70 °C for an additional 3 h (monitored by TLC). After completion of CM reaction, the reaction mixture was brought to room temperature and was added *o*-nitrobenzenesulfonyl hydrazine (*o*-NBSH) (3.6 g, 17 mmol) and Et₃N (7.3 mL, at 2 mL/g of *o*-NBSH), the reaction mixture was stirred for 12 h (Note: The reaction flask was wrapped with aluminum foil in order to avoid decomposition of *o*-NBSH due to light). A second portion of *o*-NBSH (1.8 g, 8.5 mmol) and Et₃N (3.6 mL, at 2 mL/g of *o*-NBSH) were added and the reaction mixture was stirred for an additional 8 h at room temperature. Reaction progress was monitored via crude NMR, which confirmed the

complete reduction of the external double bond in the CM adduct **4.8.2**. The reaction mixture was diluted with EtOAc (150 mL) followed by addition of saturated aqueous solution of NaHCO₃ (100 mL). The organic layer was separated and aqueous phase was extracted with EtOAc (3x100 mL). The combined organic layers were washed with brine (50 mL), dried (Na₂SO₄), concentrated under reduced pressure, and purified with flash chromatography (25% EtOAc/CH₂Cl₂), which furnished 362 mg of bicyclic phosphate **4.8.3** as a dark brown semi solid in 53% yield over three reactions in one-pot (81% av/rxn).

FTIR (neat): 2929, 2852, 2356, 1470, 1298, 1009, 1506, 1068, 972, 885, 773 cm⁻¹.

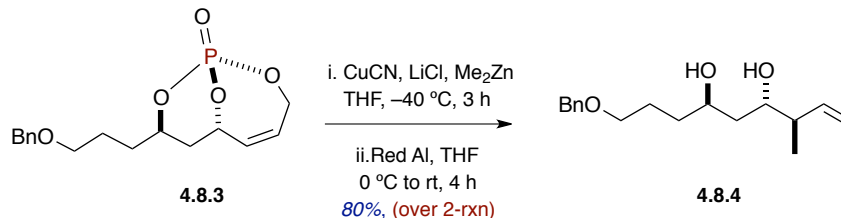
Optical Rotation: $[\alpha]_D^{23} = +45.5$ (*c* 1.72, CHCl₃).

¹H NMR (500 MHz, Chloroform-*d*): δ 7.40–7.24 (m, 5H), 5.98 (dddd, *J* = 12.0, 6.7, 3.3, 2.1 Hz, 1H), 5.54 (ddd, *J* = 11.8, 4.0, 2.5 Hz, 1H), 5.23–5.13 (m, 1H), 4.97 (ddt, *J* = 14.4, 5.6, 2.7 Hz, 1H), 4.68–4.55 (m, 1H), 4.48 (s, 2H), 4.33 (ddd, *J*_{HP} = 27.7, *J*_{HH} 14.7, 6.7 Hz, 1H), 3.50 (m, 2H), 2.16 (ddd, *J* = 14.6, 11.8, 6.2 Hz, 1H), 1.88 – 1.63 (m, 5H).

¹³C NMR (126 MHz, CDCl₃): δ 138.4, 129.9, 128.4 (2), 127.8, 127.6 (2), 127.6, 72.9, 69.6, 63.0, 62.9, 34.9 (d, *J*_{CP} = 6.0), 32.7, 32.6, 24.9.

HRMS: calculated for C₁₆H₂₁O₅P (M+Na)⁺ 347.1024; found 347.1023 (TOF MS ES+).

(3*R*,4*S*,6*R*)-9-(benzyloxy)-3-methylnon-1-ene-4,6-diol (4.84):



To a flame dried RB was added CuCN (290 mg, 3.2 mmol) and LiCl (317 mg, 7.5 mmol) inside the glove box, followed by addition of dry THF (10 mL, 0.05 M) under argon and the reaction mixture was stirred at room temperature for 15 minutes. A pale green coloration was observed. The reaction mixture was cooled to -40 °C followed by slow addition of a 1 M solution of Me₂Zn in THF (3.2 mL, 3.2 mmol). The reaction mixture was stirred for 40 minutes at -30 °C and a solution of bicyclic phosphate **4.8.3** (350 mg, 1.08 mmol) in dry THF (10 mL, 0.05 M) was added dropwise via cannula to the reaction mixture. The reaction was slowly warmed to room temperature and allowed to stir for 3 h. Upon completion of reaction (monitored via TLC), the reaction mixture was quenched with saturated aqueous ammonium chloride (NH₄Cl, 2 mL), stirred for 15 minutes followed by the addition of anhydrous Na₂SO₄ (200 mg) stirred for another 30 min. The crude product was filtered through Celite® pad and washed with excess EtOAc (3x50 mL), the filtrate was concentrated under reduce pressure, which afforded the crude acid as yellowish viscous oil, which was proceeded to the next reaction without further purification.

To a flask containing the crude acid was added THF (13.5 mL, 0.08 M). The reaction mixture was cooled to 0 °C and was added 70% solution of Red-Al in toluene (1.5 mL, 5 mmol). The reaction mixture was brought to room temperature and stirred for 4 h. After completion of reaction (monitored by TLC), it was quenched with NH₄Cl

(sat'd aq) and was added (Na_2SO_4), stirred for 30 minutes, filtered through Celite pad. The residue was washed with EtOAc (3x50 mL). The organic layer was dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The crude product was purified via flash chromatography (30% EtOAc/Hexane), which afforded TBS-protected diol **3.8.4** (240 mg, with 80% yield over two reactions) as colorless viscous oil.

FTIR (neat): 3458, 2943, 2866, 1718, 1699, 1456, 1390, 1097, 1027, 912, 842, 736, 697 cm^{-1} .

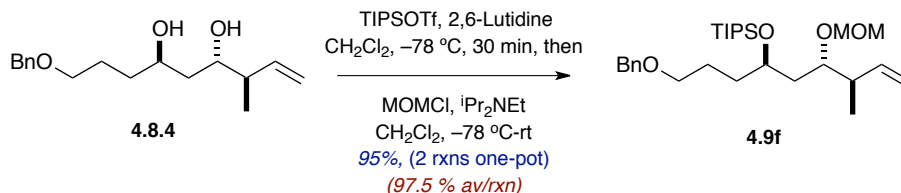
Optical Rotation: $[\alpha]_{\text{D}}^{23} = 2.1$ (c 0.8, CHCl_3).

^1H NMR (500 MHz, Chloroform- d): δ 7.42 – 7.29 (m, 5H), 5.84 – 5.72 (m, 1H), 5.20 – 5.15 (m, 1H), 5.13 (ddd, $J = 5.8, 1.9, 0.8$ Hz, 1H), 4.55 (s, 2H), 3.99–3.94 (m, 1H), 3.75 (ddd, $J = 6.7, 5.3, 3.2$ Hz, 1H), 3.65 – 3.50 (m, 2H), 3.32 (dd, $J = 4.0, 1.0$ Hz, 1H), 2.47 (dd, $J = 4.0, 1.0$ Hz, 1H), 2.36 – 2.19 (m, 1H), 1.95 – 1.72 (m, 2H), 1.73 – 1.57 (m, 4H), 1.04 (d, $J = 6.8$ Hz, 3H).

^{13}C NMR (126 MHz, CDCl_3): δ 140.6, 138.1, 128.4 (2), 127.8 (2), 127.7, 116.4, 73.1, 71.9, 70.6, 69.07, 44.4, 39.5, 34.9, 26.6, 16.1.

HRMS: calculated for $\text{C}_{17}\text{H}_{26}\text{O}_3$ ($\text{M}+\text{Na}$) $^+$ 301.1780; found 301.1781 (TOF MS ES+).

(5*S*,7*R*)-7-(3-(benzyloxy)propyl)-5-((*R*)-but-3-en-2-yl)-9,9-diisopropyl-10-methyl-2,4,8-trioxa-9-silaundecane (4.9f):



To a solution of **4.8.4** (240 mg, 0.86 mmol) in CH_2Cl_2 (8.6 mL, 0.1 M) was added 2,6 lutidine (251 μL , 2.1 mmol). The reaction mixture was cooled to $-78\text{ }^\circ\text{C}$ and was added dropwise TIPSOTf (254 μL , 0.9 mmol). The reaction mixture was stirred for 30 min, after completion of reaction (monitored via TLC), it was added *N,N*-disopropylethylamine (600 μL , 3.44 mmol) followed by dropwise addition of chloro(methoxy)methane (130 μL , 1.72 mmol) and the reaction mixture was stirred for 12 h. After completion of reaction, it was quenched with saturated aqueous NaHCO_3 , extracted with CH_2Cl_2 , dried (MgSO_4), concentrated under reduced pressure. The crude product was purified using silica gel column chromatography (5% EtOAc/Hexanes), which furnished 394 mg of **4.9f** in 95% yield over two reactions in one-pot (97.5% av/rxn) as colorless viscous liquid.

FTIR (neat): 2943, 2866, 2352, 2329, 1693, 1556, 1454, 1348, 1151, 1099, 1041, 916, 883, 732 cm^{-1} .

Optical Rotation: $[\alpha]_{\text{D}}^{23} = -1.25$ (*c* 1.43, CHCl_3).

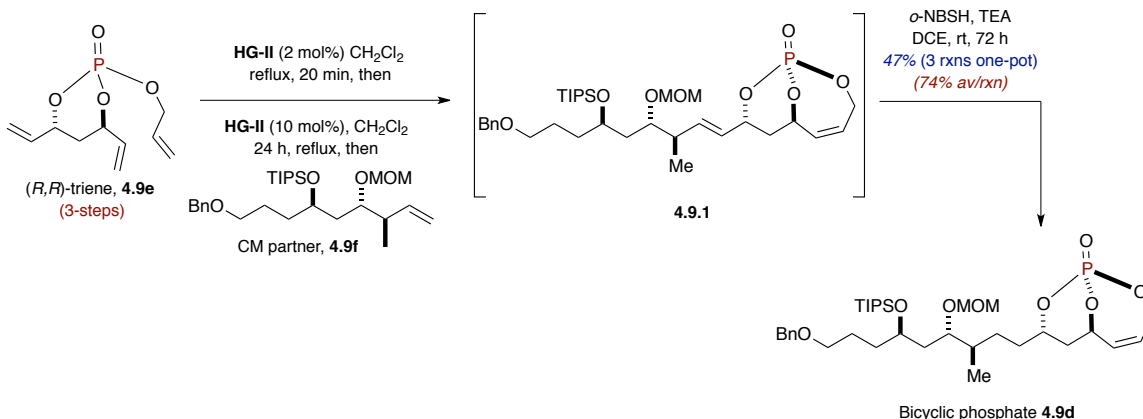
^1H NMR (500 MHz, Chloroform-*d*): δ 7.41 – 7.29 (m, 5H), 5.85 – 5.75 (m, 1H), 5.10 – 5.03 (m, 2H), 4.77 – 4.63 (m, 2H), 4.52 (s, 2H), 4.02–3.99 (m, 1H), 3.69 (dt, *J* = 7.7, 3.8

Hz, 1H), 3.49 (t, $J = 6.4$ Hz, 2H), 3.39 (s, 3H), 2.59 – 2.48 (m, 1H), 2.20 (s, 1H), 1.83 – 1.47 (m, 6H), 1.07 (s, 23H).

^{13}C NMR (126 MHz, CDCl_3): δ 140.2, 138.7, 128.3 (2), 127.5 (2), 127.4, 114.9, 96.7, 79.7, 72.7, 70.6, 69.8, 55.7, 41.3, 38.4, 34.3, 24.8, 18.3 (6), 14.2, 12.9 (3).

HRMS: calculated for $\text{C}_{28}\text{H}_{50}\text{O}_4\text{Si}$ ($\text{M}+\text{Na}$) $^+$ 501.3376; found 501.3375 (TOF MS ES $^+$).

(1*R*,6*R*,8*S*)-8-((3*R*,4*S*,6*R*)-9-(benzyloxy)-4-(methoxymethoxy)-3-methyl-6-((triisopropylsilyl)oxy)nonyl)-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-ene 1-oxide (4.9d):



To a solution of (*S,S*)-triene **4.9e** (394 mg, 1.7 mmol) in a degassed CH_2Cl_2 (347 mL, 0.005 M) was added **HG-II** (21.2 mg, 0.034 mmol, 2 mol%) the reaction mixture was refluxed for 20 min. After completion of RCM reaction, CH_2Cl_2 was evaporated under reduced pressure. To the crude product was added freshly distilled, freeze-degas-thawed 1,2-dichloroethane (DCE) (17 mL, 0.1 M), the CM partner **4.9f** (975 mg, 2.04 mmol) and HG-II (63 mg, 0.102 mmol, 6 mol%) under inert atmosphere. The reaction mixture was stirred at 70 °C for 12 h, a second portion of HG-II (21 mg, 0.034 mmol, 2 mol%) and CM partner (162 mg, 0.34 mmol) were added to the reaction mixture, was stirred at 70 °C for 8 h and a third portion of HG-II (21 mg, 0.034 mmol, 2 mol%) and

CM partner (162 mg, 0.34 mmol) were added and the reaction mixture was stirred for an additional 8 h. After completion of CM reaction, the crude product **4.9.1** was subjected to chemoselective hydrogenation “H₂” reaction using *o*-NBSH and Et₃N (2 mL/1 g of *o*-NBSH) at room temperature. It should be noted that for the chemoselective hydrogenation of external olefin of the crude CM product **4.9.1**, *o*-NBSH (1.8 g, 8.5 mmole) and Et₃N (3.6 mL, 2 mL/1 g of *o*-NBSH) were sequentially added after each 8–12 h and the reaction mixture was stirred for 72 h. Reaction progress was monitored via crude NMR, which confirmed the complete reduction of external double bond in the CM adduct **4.9.1**. The reaction mixture was diluted with EtOAc (100 mL) followed by addition of saturated aqueous solution of NaHCO₃ (50 mL). The organic layer was separated and aqueous phase was extracted with EtOAc (3x100 mL). The combined organic layers were washed with brine (50 mL), dried (Na₂SO₄), concentrated under reduced pressure, and purified with flash chromatography (40% EtOAc/Hexane), which furnished 362 mg of bicyclic phosphate **4.8.3** as a dark brown semi solid in 47% yield over three reactions in one-pot (74% av/rxn).

FTIR (neat): 2945, 2864, 2351, 1556, 1305, 1245, 1101, 1039, 972, 773 cm⁻¹.

Optical Rotation: $[\alpha]_D^{23} = -24.3.0$ (*c* 0.63, CHCl₃).

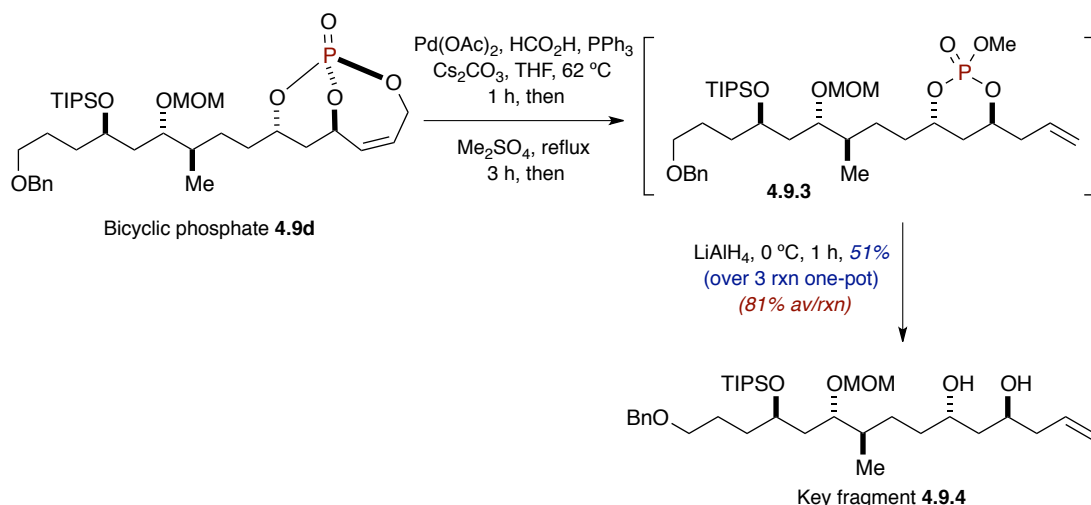
¹H NMR (500 MHz, Chloroform-*d*): δ 7.38 – 7.30 (m, 5H), 6.05 (dddd, *J* = 12.0, 6.8, 3.2, 2.1 Hz, 1H), 5.59 (ddd, *J* = 11.9, 3.9, 2.5 Hz, 1H), 5.24–5.15 (m, 1H), 5.02 (dddd, *J* = 14.8, 8.5, 5.0, 2.6 Hz, 1H), 4.70 – 4.62 (m, 2H), 4.61 – 4.54 (m, 1H), 4.52 (s, 2H), 4.38 (ddd, *J*_{HP} = 27.7, *J*_{HH} 14.8, 6.7 Hz, 1H), 4.02–3.96 (m, 1H), 3.65 (dt, *J* = 8.9, 3.0 Hz, 1H), 3.50 (td, *J* = 6.2, 1.8 Hz, 2H), 3.37 (d, *J* = 5.4 Hz, 4H), 2.23 – 2.13 (m, 1H), 1.90 – 1.78

(m, 1H), 1.78 – 1.49 (m, 6H), 1.43 (ddd, $J = 14.2, 8.2, 2.8$ Hz, 1H), 1.28 (d, $J = 3.0$ Hz, 0H), 1.24 – 1.14 (m, 1H), 1.07 (d, $J = 6.0$ Hz, 25H), 0.92 (d, $J = 6.8$ Hz, 3H).

^{13}C NMR (126 MHz, CDCl_3): δ 138.6, 129.8, 128.3 (2), 128.0, 127.5 (2), 127.5, 96.9, 80.1, 72.8, 70.6, 70.1, 63.0 (d, $J_{\text{CP}} = 6.5$), 62.9, 55.6, 37.8, 36.5, 34.7 (d, $J_{\text{CP}} = 4.1$), 34.6, 33.7 (d, $J_{\text{CP}} = 6.0$), 27.6, 25.1, 18.3 [6C, Si ($\text{CH}(\text{CH}_3)_2$)₃], 14.3, 13.0, 12.9 [3C, Si ($\text{CH}(\text{CH}_3)_2$)₃].

HRMS: calculated for $\text{C}_{34}\text{H}_{59}\text{O}_8\text{PSi}$ ($\text{M}+\text{Na}$)⁺ 677.3615; found 677.3615 (TOF MS ES+).

(4*S*,6*S*,9*R*,10*S*,12*R*)-15-(benzyloxy)-10-(methoxymethoxy)-9-methyl-12-((triisopropylsilyl)oxy)pentadec-1-ene-4,6-diol (4.9.4):



To a stirring solution of bicyclic phosphate **4.9d** (1.2 g, 1.8 mmol) in dry THF (6.1 mL, 0.3 M) under argon was added Cs_2CO_3 (2.9 g, 9 mmol) and HCO_2H (2.23 mL, 4.8 mmol). Then a solution of 5 mol % $\text{Pd}(\text{OAc})_2$ (29 mg, .09 mmol) and PPh_3 (47 mg, 0.18 mmol) in dry THF (1.6 mL) under argon was immediately transferred *via* cannula to the reaction mixture. The reaction mixture was stirred at 60°C for 1 h (monitored by TLC). After 1 h, the starting materials were consumed (indicated by TLC) and the color of the reaction mixture was turned black. After complete of reaction, dimethylsulfate

(Me₂SO₄) (525 μl, 5.4 mmol) was added and the reaction mixture was refluxed for 3 h (TLC showed that phosphate acid was completely methylated). The reaction mixture was cooled to 0 °C and LiAlH₄ (205 mg, 5.4 mmol) was added portion-wise over a period of five minutes. The reaction mixture was stirred at 0 °C for 1 h. After completion of reduction, it was quenched following the Fieser workup¹¹ *via* slow sequential addition of H₂O (1 mL/g of LiAlH₄), followed by 10% aqueous NaOH (1 mL/g of LiAlH₄) and finally H₂O (3 mL/g of LiAlH₄). The ice bath was removed and the reaction mixture was stirred for 2 h at room temperature. The reaction mixture was filtered through Celite® pad, the solid residue was washed with excess EtOAc and dried (Na₂SO₄). The resulting solution was concentrated under reduced pressure and purified using a short silica gel chromatography column (hexane/EtOAc 2:1), which afforded the 550 mg of 1,3-*anti* diol fragment **4.9.4** in 51% yield over 3 reactions in one-pot (83% av/rxn) as a colorless viscous liquid.

FTIR (neat): 3417, 2931, 2864, 1699, 1556, 1454, 1359, 1207, 1095, 1093, 883, 734 cm⁻¹.

Optical Rotation: $[\alpha]_D^{23} = -1.38$ (*c* 0.95, CHCl₃).

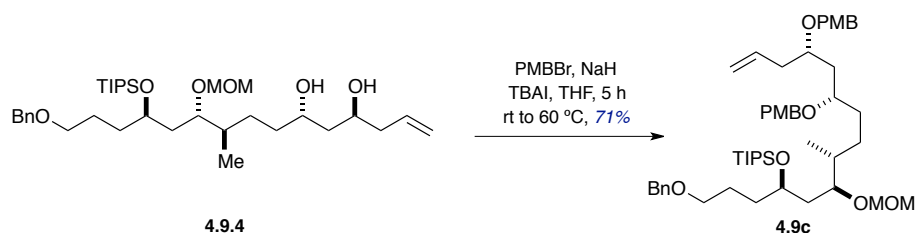
¹H NMR (500 MHz, Chloroform-*d*): δ 7.39 – 7.29 (m, 5H), 5.89–5.79 (m, 1H), 5.22–5.13 (m, 2H), 4.70–4.65 (m, 2H), 4.53 (s, 2H), 4.01 (td, *J* = 7.1, 3.6 Hz, 2H), 3.97–3.90 (m, 1H), 3.67 (dt, *J* = 8.9, 3.1 Hz, 1H), 3.49 (t, *J* = 6.1 Hz, 2H), 3.38 (s, 3H), 2.40 – 2.22 (m, 4H), 1.89 – 1.78 (m, 1H), 1.78 – 1.55 (m, 6H), 1.55 – 1.43 (m, 3H), 1.10–1.05 (m, 21H), 0.93 (d, *J* = 6.8 Hz, 3H).

[11]. L. F. Fieser, M. Fieser in *Reagents for Organic Synthesis*, Vol. 1, Wiley: New York, **1967**, pp. 581–595; b) V. M. Mićović, M. Mihailović, *J. Org. Chem.* **1953**, 18, 1190–1200.

^{13}C NMR (126 MHz, CDCl_3): δ 138.8, 130.0, 128.5 (Aromatic 2 x CH), 128.2, 127.7 (Aromatic CH x 2), 127.7, 97.1, 80.3, 73.0, 70.8, 70.2, 63.2, 63.1, 55.8, 38.0, 36.7, 35.4, 34.9, 33.9, 27.8, 25.3, 18.5 [$6\times\text{CH}_3$, $\text{Si}-(\text{CH}(\underline{\text{CH}_3})_2)_3$], 14.5, 13.2, 13.1 [$3\times\text{CH}$, $\text{Si}-(\underline{\text{CH}}(\text{CH}_3)_2)_3$].

HRMS: calculated for $\text{C}_{34}\text{H}_{62}\text{O}_6\text{Si}$ ($\text{M}+\text{Na}$) $^+$ 617.4213; found 617.4213 (TOF MS ES $^+$).

(5*S*,7*R*)-7-(3-(benzyloxy)propyl)-5-((2*R*,5*S*,7*S*)-5,7-bis((4-methoxybenzyl)oxy)dec-9-en-2-yl)-9,9-diisopropyl-10-methyl-2,4,8-trioxa-9-silaundecane (4.9c):



To a stirred solution of 1,3-*anti* diol fragment **4.9.4** (500 mg, 0.84 mmol) in dry THF (10.5 ML, 0.08 M) was added NaH (100 mg, 4.2 mmol), and the reaction mixture was stirred for 30 min at room temperature. Then, it was added *p*-methoxy benzyl bromide (675 mg, 3.36 mmol) and tetrabutylammonium iodide (30 mg, 0.08 mmol) and the reaction mixture was stirred at 60 °C for 12 h. After completion of reaction (monitored by TLC), it was quenched with saturated aqueous solution of NaHCO_3 (10 mL), extracted with EtOAc (3x100), dried (Na_2SO_4), concentrated under reduced pressure, and purified with flash chromatography (25% EtOAc/Hexane), which afforded 502 mg of olefin **4.9c** in 71% yield as a colorless viscous liquid.

FTIR (neat): 2935, 2864, 2329, 1614, 1512, 1461, 1359, 1299, 1247, 1170, 1035, 819, 769 cm^{-1} .

Optical Rotation: $[\alpha]_{\text{D}}^{23} = +19.7$ (c 0.87, CHCl_3).

^1H NMR (500 MHz, Chloroform- d): δ 7.30 – 7.20 (m, 5H), 7.17 – 7.11 (m, 4H), 6.81 – 6.74 (m, 4H), 5.76 (m, 1H), 5.06 – 4.95 (m, 2H), 4.59 – 4.55 (m, 2H), 4.49 – 4.34 (m, 4H), 4.16 (dd, $J = 18.5, 11.0$ Hz, 2H), 3.91 (td, $J = 7.3, 3.6$ Hz, 1H), 3.76 – 3.72 (m, 1H), 3.70 (s, 6H), 3.63 (dt, $J = 9.2, 4.7$ Hz, 1H), 3.58 – 3.51 (m, 2H), 3.40 (td, $J = 6.1, 1.6$ Hz, 2H), 3.28 (s, 3H), 2.30 – 2.21 (m, 2H), 1.77 – 1.14 (m, 12H), 1.01–0.95 (m, 23H), 0.81 (d, $J = 6.8$ Hz, 3H).

^{13}C NMR (126 MHz, CDCl_3): δ 159.0 (Aromatic 2 x CH), 138.7, 134.7, 131.1, 131.0, 129.4 (Aromatic 2 x CH), 129.3 (Aromatic 2 x CH), 128.3 (Aromatic 2 x CH), 127.5 (Aromatic 2 x CH), 127.4, 117.2, 113.7 (Aromatic 2 x CH), 96.8, 80.6, 75.4, 74.7, 72.8, 70.7, 70.6, 70.5, 70.0, 55.7, 55.3, 55.3, 55.2, 39.9, 38.6, 37.5, 37.0, 34.7, 32.1, 27.8, 25.0, 18.4 [6xCH₃, Si-(CH(CH₃)₂)₃], 18.3, 14.1, 13.0 [3xCH, Si(CH(CH₃)₂)₃].

HRMS: calculated for $\text{C}_{50}\text{H}_{78}\text{O}_8\text{Si}$ ($\text{M}+\text{Na}$)⁺ 857.5364; found 857.5364 (TOF MS ES+).

(5*R*,7*S*,10*R*,11*S*,13*R*)-ethyl-16-(benzyloxy)-5,7-bis((4-methoxybenzyl)oxy)-11-(methoxymethoxy)-10-methyl-3-oxo-13-((triisopropylsilyl)oxy)hexadecanoate (4.10.2):



To a stirring solution of olefin **4.9c** (400 mg, 0.47 mmol) in dioxane-water (3:1, 6 mL, 0.08 M) were added 2,6-lutidine (109 μ L, 0.94 mmol), OsO₄ (4% in water, 3 mg, 0.011 mmol), and NaIO₄ (400 mg, 1.88 mmol). The reaction mixture was stirred at room temperature and monitored by TLC. After completion of reaction, water (6 mL) and CH₂Cl₂ (12 mL) were added. Both layers were separated, and the aqueous layer was extracted with CH₂Cl₂ (3x15 mL). The combined organic layer was washed with brine and dried (MgSO₄). The solvent was removed under reduced pressure and the crude aldehyde was proceeded in to the next step without any further purification.

To a solution of crude aldehyde in CH₂Cl₂ (6 mL, 0.07 M) was added ethyl diazoacetate (121 μ L, 1.175 mmol), NaHCO₃ (197 mg, 2.35 mmol) and SnCl₄·5H₂O (65 mg, 0.188 mmol). The reaction mixture was stirred at room temperature for 2 h. After completion of reaction, it was quenched with brine (10 mL). The organic layer was extracted with Et₂O (3x30 mL). The combined organic extracts were washed with brine, dried (Na₂SO₄), and concentrated under reduced pressure. The residue was purified by flash chromatography using EtOAc/Hexane (5: 95) to afford β -keto ester **4.10.2** (315 mg, 69%) as colorless oil and as a mixture of keto and enolic tautomers.

FTIR (neat): 2941, 2864, 1743, 1718, 1612, 1514, 1464, 1365, 1301, 1247, 1172, 1037, 918, 883, 819, 736, 698 cm^{-1} .

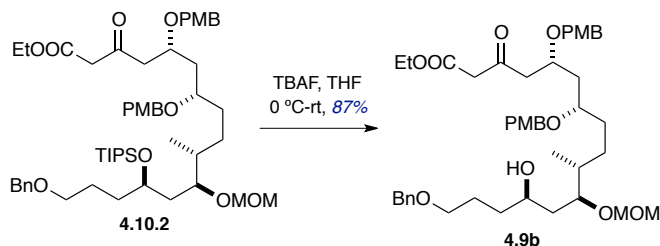
Optical Rotation: $[\alpha]_{\text{D}}^{23} = +16.3$ (c 0.87, CHCl_3).

^1H NMR (500 MHz, Chloroform- d): δ 7.39 – 7.28 (m, 5H), 7.26 – 7.18 (m, 4H), 6.94 – 6.81 (m, 4H), 4.70 – 4.60 (m, 3H), 4.53 – 4.39 (m, 4H), 4.34 – 4.16 (m, 4H), 4.13 (ddd, J = 8.3, 4.1, 2.4 Hz, 1H), 4.02–3.94 (m, 1H), 3.82 (s, 2H), 3.78 (s, 6H), 3.67 – 3.62 (m, 1H), 3.57 (ddd, J = 7.6, 3.1, 1.5 Hz, 1H), 3.50 – 3.46 (m, 2H), 3.43 (s, 2H), 3.36 (d, J = 1.5 Hz, 3H), 2.85 – 2.67 (m, 2H), 1.85 – 1.32 (m, 10H), 1.27 (t, J = 7.1 Hz, 3H), 1.06 (m, 21H), 0.90 (d, J = 6.8 Hz, 3H).

^{13}C NMR (126 MHz, CDCl_3): δ 201.8, 167.3, 159.3 (Aromatic 2xCH), 138.8, 133.3, 131.0 (Aromatic 2xCH), 129.5, 128.9, 128.5, 127.7 (Aromatic 2xCH), 114.1 (Aromatic 2xCH), 113.9, 97.0, 80.7, 75.7, 73.0, 72.7, 71.8, 70.8, 70.4, 70.2, 65.3, 61.5, 60.2, 55.9, 55.5, 55.5, 55.4, 50.5, 48.9, 40.5, 37.7, 37.2, 34.9, 32.2, 28.0, 25.2, 18.6, 18.5 [6x CH_3 , Si-(CH ($\underline{\text{C}}\text{H}_3$) $_2$) $_3$], 14.3, 13.2 [3xCH, Si ($\underline{\text{C}}\text{H}$ (CH_3) $_2$) $_3$].

HRMS: calculated for $\text{C}_{53}\text{H}_{82}\text{O}_{11}\text{Si}$ ($\text{M}+\text{Na}$) $^+$ 952.5624; found 952.5622 (TOF MS ES+).

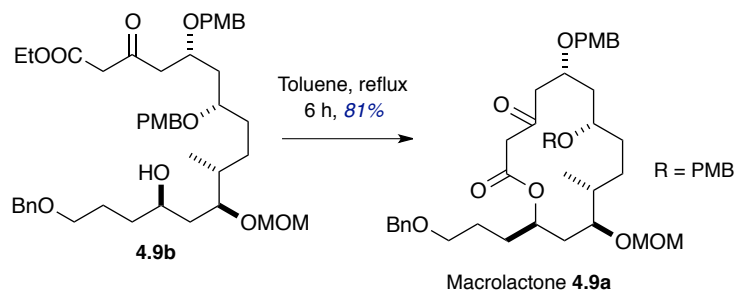
(5*R*,7*S*,10*R*,11*S*,13*R*)-ethyl-16-(benzyloxy)-13-hydroxy-5,7-bis((4-methoxybenzyl)oxy)-11-(methoxymethoxy)-10-methyl-3-oxohexadecanoate (4.9b)



To a stirring solution of TIPS-protected alcohol **4.10.2** (300 mg, 0.32 mmol) in dry THF (4 mL, 0.08 M) was added TBAF (184 μ L, 0.64 mmol) at 0 °C. The reaction mixture was stirred at 40 °C for 12 h. After completion of reaction (monitored via TLC), it was quenched with NH₄Cl. The organic layer was extracted with EtOAc (3x20 mL). The combined organic extracts were washed with brine, dried (Na₂SO₄), and concentrated under reduced pressure. The residue was purified by silica gel chromatography using EtOAc/Hexane (25: 75) to afford alcohol **4.9b** (222 mg, 87%) as colorless oil.¹²

[12]. Structural characterization data for compound, 4.9bc and 4.9a is not provided as we have only the mass and ¹HNMR available for these compounds.

(6*R*,8*S*,11*R*,12*S*,14*R*)-14-(3-(benzyloxy)propyl)-6,8-bis((4-methoxybenzyl)oxy)-12-(methoxymethoxy)-11-methyloxacyclotetradecane-2,4-dione (4.9a**):**



To a stirring solution of alcohol **4.9a** (50 mg, 0.065 mmol) in dry toluene (65 mL, 0.001 M) was taken in a Dean-Stark apparatus and refluxed for 12 h with azeotropic removal of the EtOH as a by-product. After completion of the reaction (monitored by TLC), the solvent was removed under reduced pressure. The residue was purified by flash chromatography using EtOAc/Hexane (15:85) to afford macrolactone **4.9a** (37.5 mg, 81%) as colorless oil.

Special Acknowledgment

The author acknowledges that portions of this chapter, including the chemical procedures, spectral data are reprinted, in part, or adapted from the following publications, with permission from the corresponding publishers:

(a) Javed, S.; Bodugam, M.; Ganguly, A.; Torres, J.; Hanson, P. R. Modular Synthesis of Novel Macrocycles Bearing α,β -Unsaturated Chemotypes via a Series of One-Pot, Sequential Protocols. *Chem. Eur. J.* **2016**, 22, 6755–6758. (b) Bodugam, M.; Javed, S.; Ganguly, A.; Torres, J.; Hanson, P. R. A Pot-Economical Approach to the Total Synthesis of Sch-725674. *Org. Lett.* **2016**, 18, 516–519. (c) Maitra, S.; Bodugam, M.; Javed, S. Hanson, P. R. Efficient Synthesis of the C9–C25 Subunit of Spirastrellolide B. *Org. Lett.* **2016**, 18, 3094–3097.

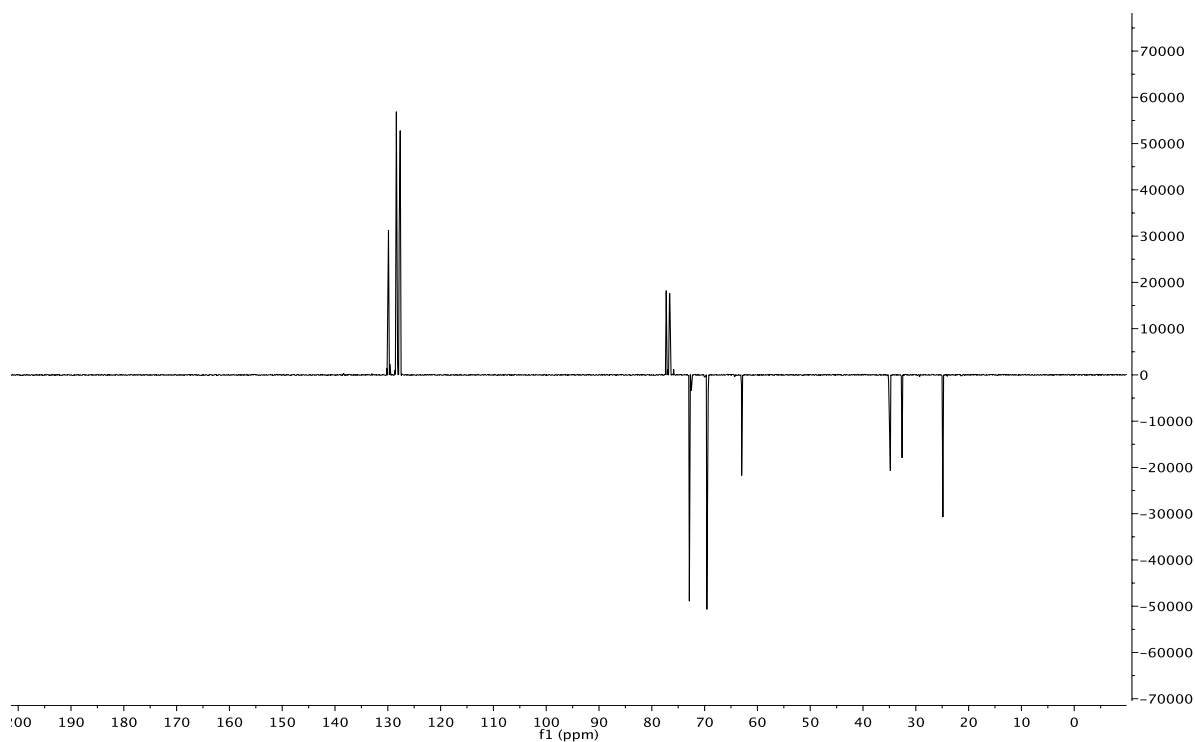
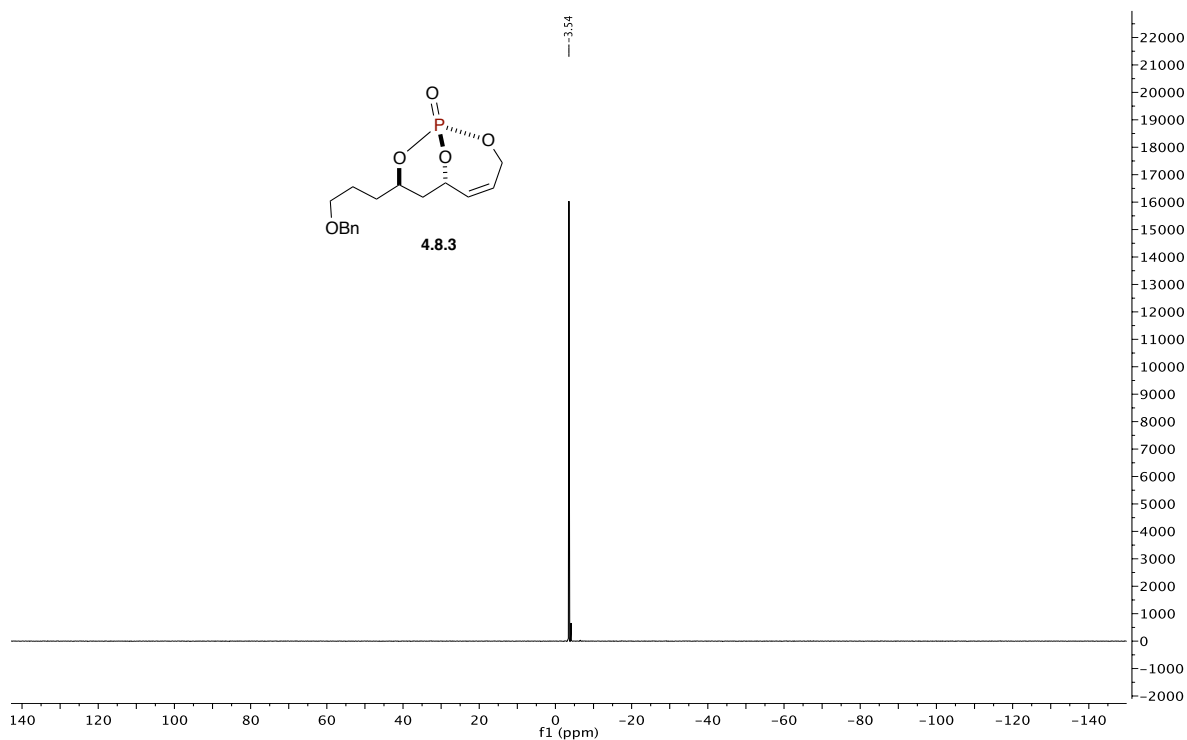
Chemical structure of **4.8.3** is shown above the spectrum. The structure is a bicyclic phosphonate derivative with a benzyl (OBn) group and a vinyl group.

¹H NMR spectrum (CDCl₃) of **4.8.3**. The x-axis represents the chemical shift in ppm (δ), ranging from -0.5 to 9.0. The y-axis represents the intensity in arbitrary units, ranging from 0 to 20,000. Integration values are provided below the baseline.

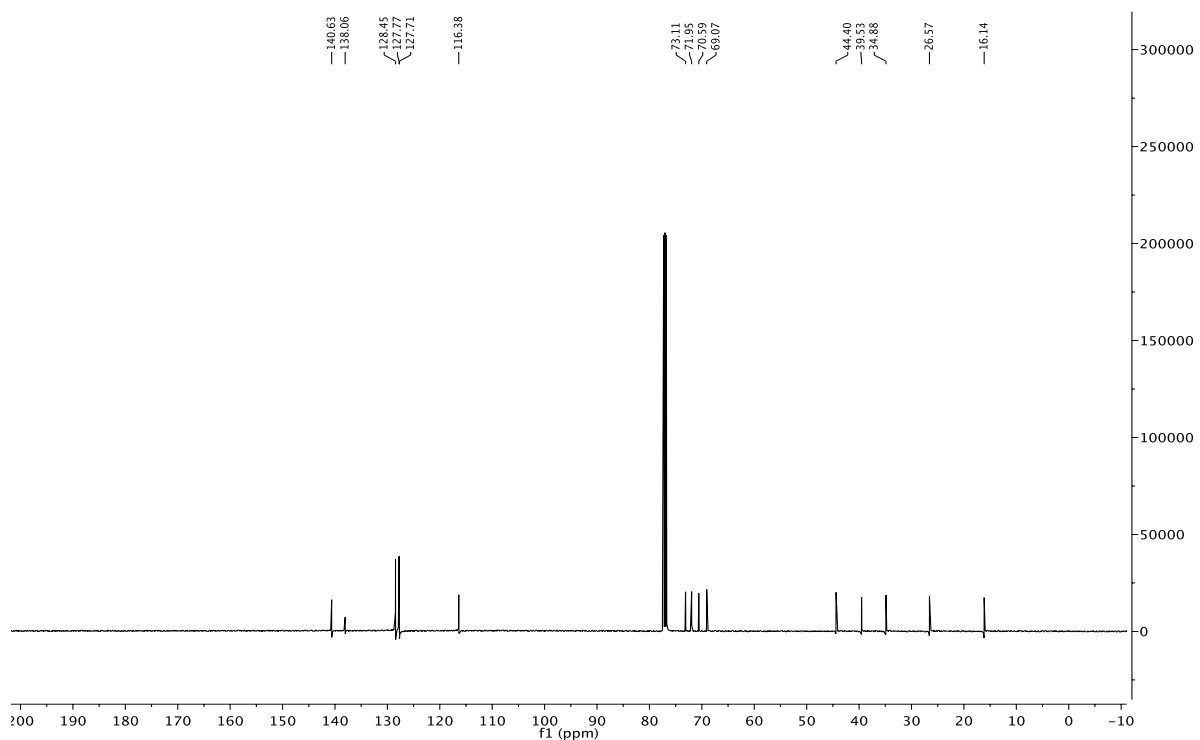
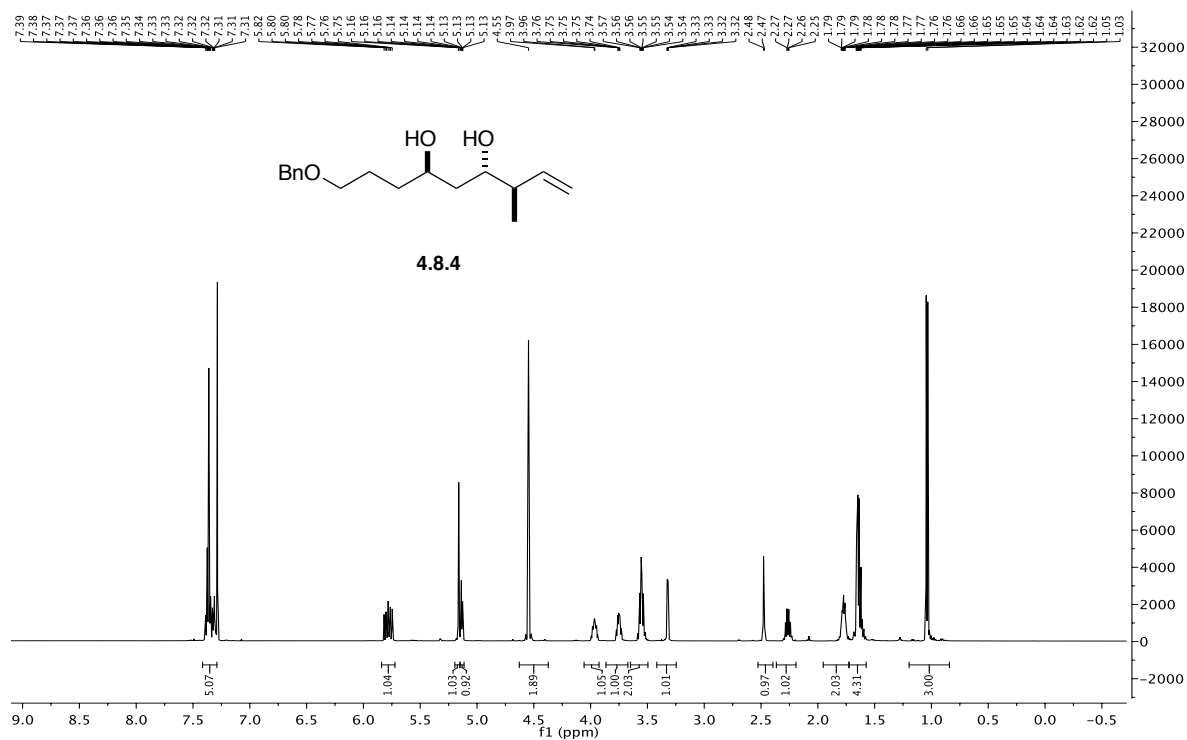
Integration values (from left to right): 5.14, 1.00, 0.92, 1.01, 1.01, 0.94, 1.90, 1.03, 1.87, 0.97, 4.99.



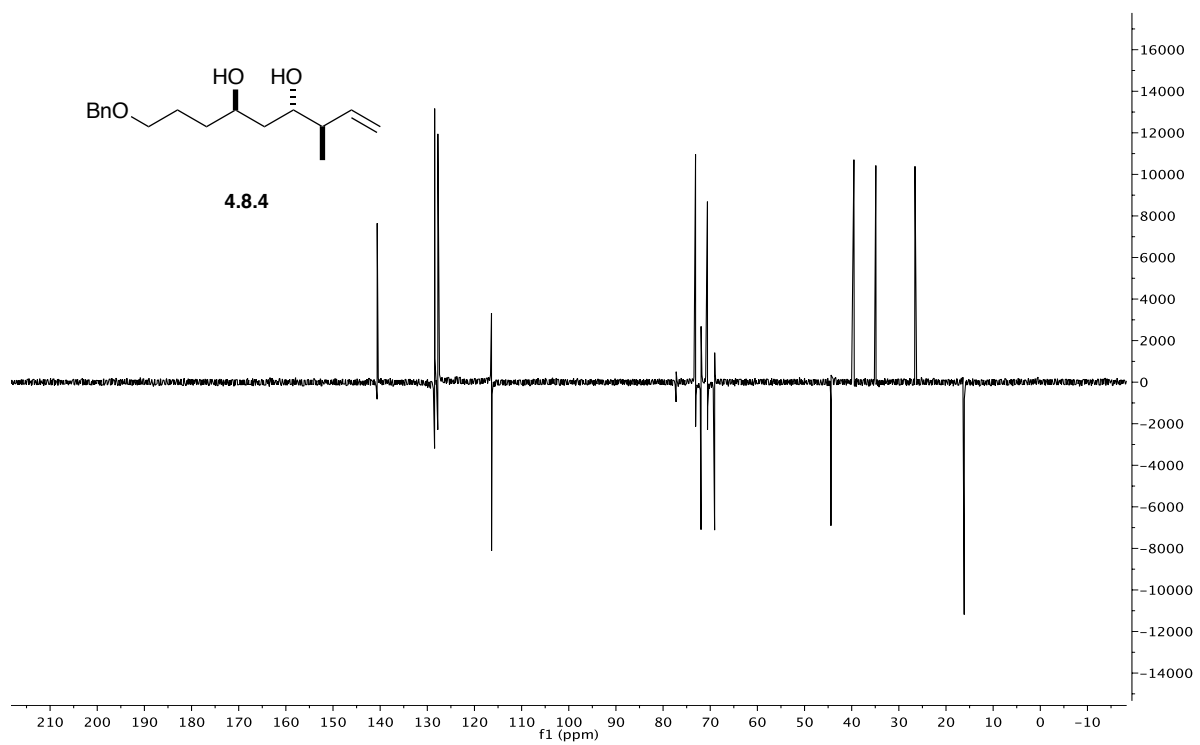
(1*S*,6*S*,8*R*)-8-(3-(benzyloxy)propyl)-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-ene 1-oxide (4.8.3) (4.8.3):



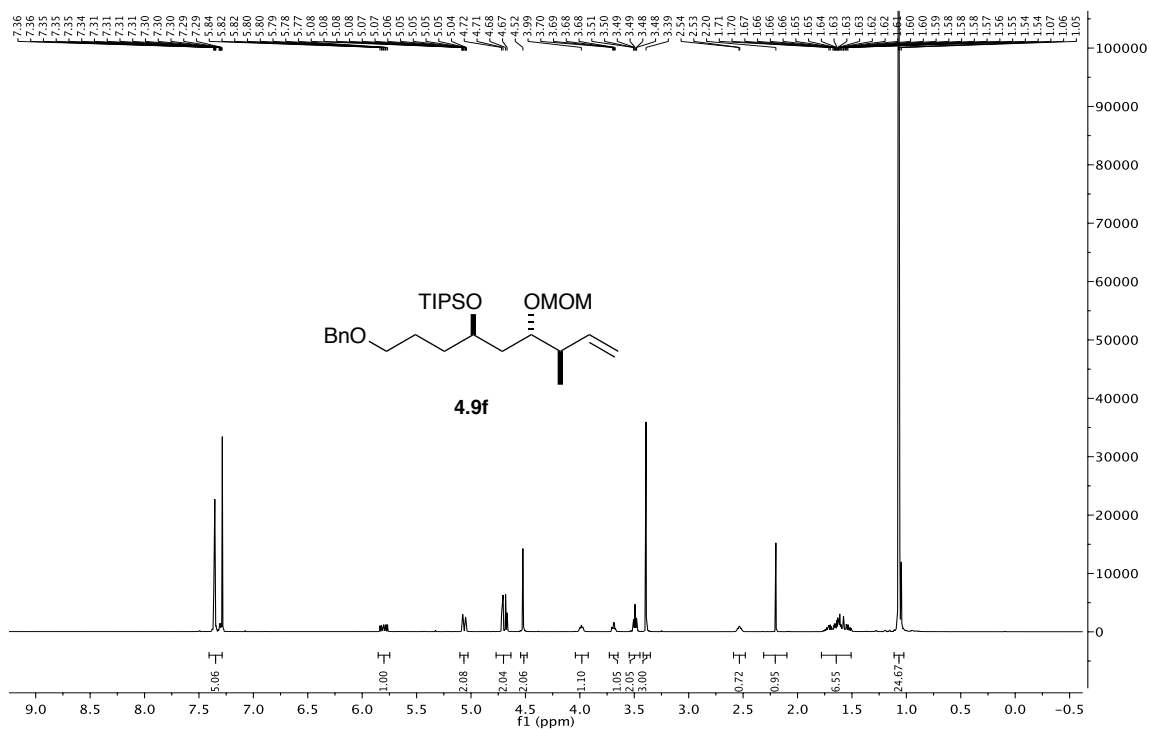
(3*R*,4*S*,6*R*)-9-(benzyloxy)-3-methylnon-1-ene-4,6-diol (4.84):



(3*R*,4*S*,6*R*)-9-(benzyloxy)-3-methylnon-1-ene-4,6-diol (4.84):



(5*S*,7*R*)-7-(3-(benzyloxy)propyl)-5-((*R*)-but-3-en-2-yl)-9,9-diisopropyl-10-methyl-2,4,8-trioxa-9-silaundecane (4.9f):



2,15-trioxo-9-shaandecane (4.9f).

Chemical structure of 2,15-trioxo-9-shaandecane (4.9f) is shown above the spectrum. The structure is a 10-membered ring with a BnO group at position 2, a TIPSO group at position 9, and an OMOM group at position 15. The structure is labeled 4.9f.

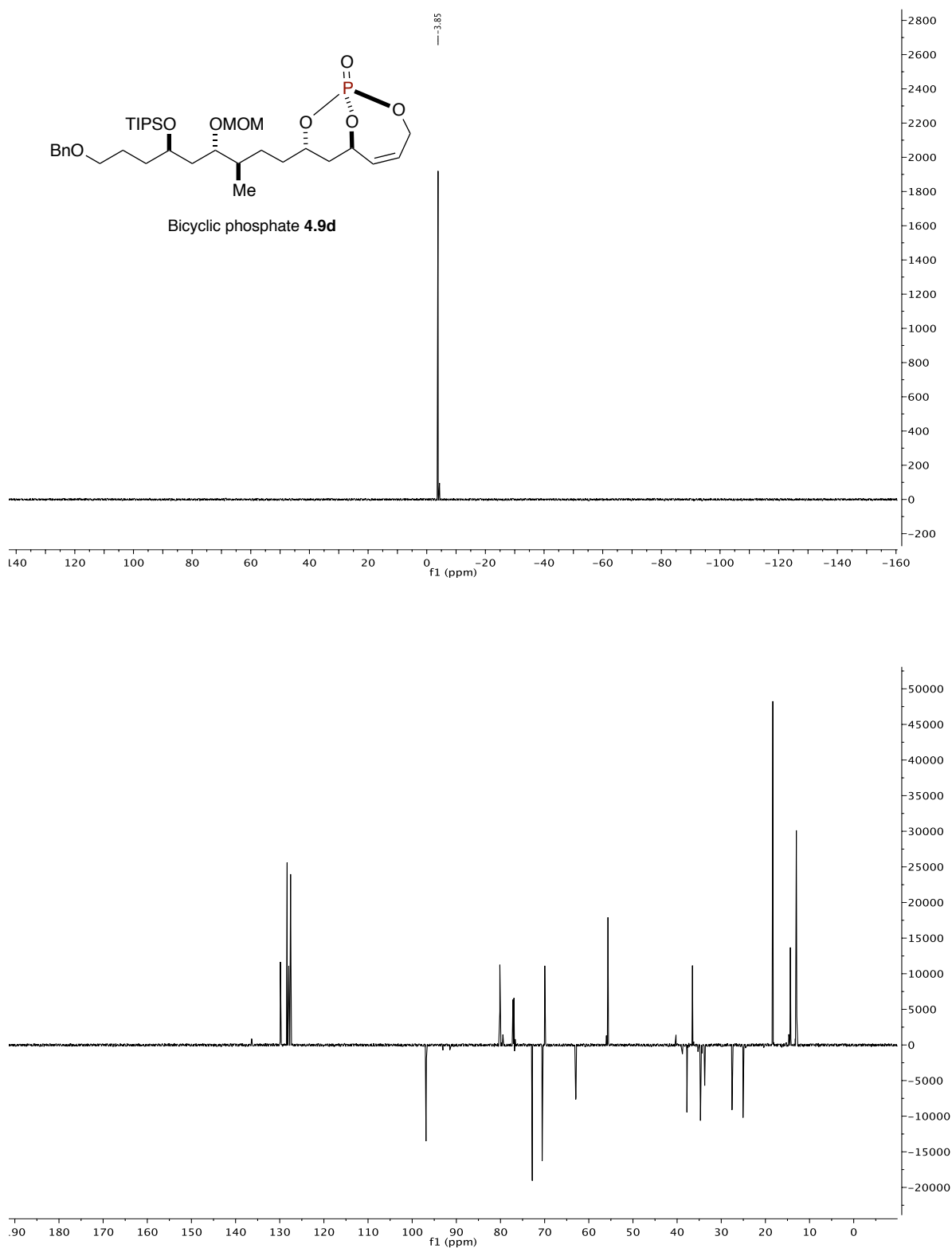
Bicyclic phosphate 4.9d

¹H NMR spectrum (400 MHz, CDCl₃) of Bicyclic phosphate 4.9d. The spectrum shows peaks from 9.0 to -0.5 ppm. The chemical structure of 4.9d is shown above the spectrum. The structure is a bicyclic phosphate with a BnO group, a TIPSO group, an OMOM group, and a Me group. The spectrum includes integration values below the peaks.

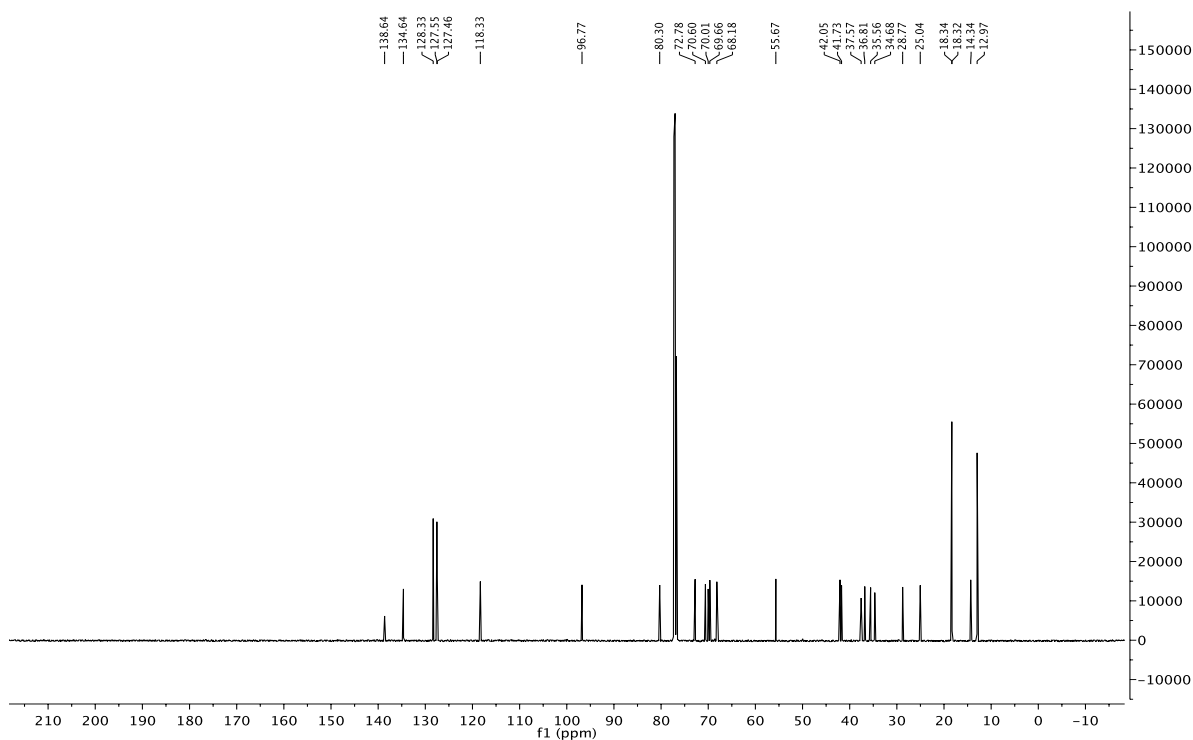
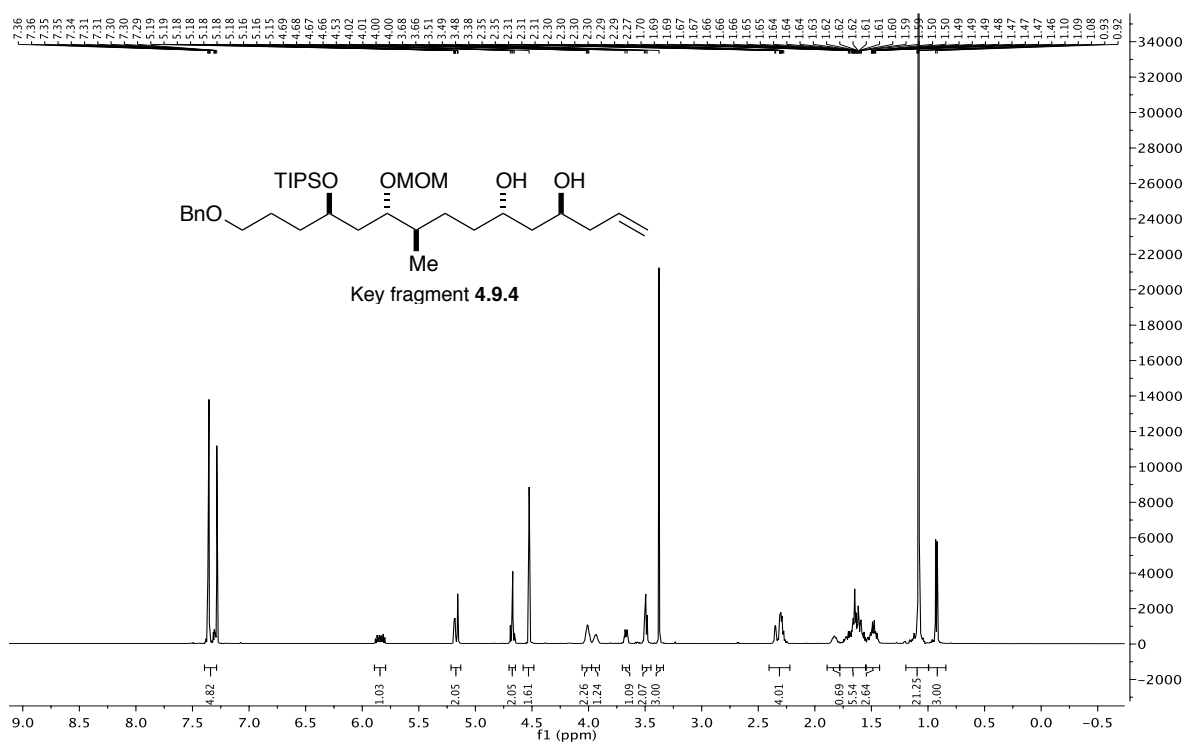
Chemical Shift (ppm)	Integration
7.36, 7.35, 7.34, 7.31, 7.30, 7.29, 7.28, 7.27, 7.26, 7.25, 7.24, 7.23, 7.22, 7.21, 7.20, 7.19, 7.18, 7.17, 7.16, 7.15, 7.14, 7.13, 7.12, 7.11, 7.10, 7.09, 7.08, 7.07, 7.06, 7.05, 7.04, 7.03, 7.02, 7.01, 7.00, 6.99, 6.98, 6.97, 6.96, 6.95, 6.94, 6.93, 6.92, 6.91, 6.90, 6.89, 6.88, 6.87, 6.86, 6.85, 6.84, 6.83, 6.82, 6.81, 6.80, 6.79, 6.78, 6.77, 6.76, 6.75, 6.74, 6.73, 6.72, 6.71, 6.70, 6.69, 6.68, 6.67, 6.66, 6.65, 6.64, 6.63, 6.62, 6.61, 6.60, 6.59, 6.58, 6.57, 6.56, 6.55, 6.54, 6.53, 6.52, 6.51, 6.50, 6.49, 6.48, 6.47, 6.46, 6.45, 6.44, 6.43, 6.42, 6.41, 6.40, 6.39, 6.38, 6.37, 6.36, 6.35, 6.34, 6.33, 6.32, 6.31, 6.30, 6.29, 6.28, 6.27, 6.26, 6.25, 6.24, 6.23, 6.22, 6.21, 6.20, 6.19, 6.18, 6.17, 6.16, 6.15, 6.14, 6.13, 6.12, 6.11, 6.10, 6.09, 6.08, 6.07, 6.06, 6.05, 6.04, 6.03, 6.02, 6.01, 6.00, 5.99, 5.98, 5.97, 5.96, 5.95, 5.94, 5.93, 5.92, 5.91, 5.90, 5.89, 5.88, 5.87, 5.86, 5.85, 5.84, 5.83, 5.82, 5.81, 5.80, 5.79, 5.78, 5.77, 5.76, 5.75, 5.74, 5.73, 5.72, 5.71, 5.70, 5.69, 5.68, 5.67, 5.66, 5.65, 5.64, 5.63, 5.62, 5.61, 5.60, 5.59, 5.58, 5.57, 5.56, 5.55, 5.54, 5.53, 5.52, 5.51, 5.50, 5.49, 5.48, 5.47, 5.46, 5.45, 5.44, 5.43, 5.42, 5.41, 5.40, 5.39, 5.38, 5.37, 5.36, 5.35, 5.34, 5.33, 5.32, 5.31, 5.30, 5.29, 5.28, 5.27, 5.26, 5.25, 5.24, 5.23, 5.22, 5.21, 5.20, 5.19, 5.18, 5.17, 5.16, 5.15, 5.14, 5.13, 5.12, 5.11, 5.10, 5.09, 5.08, 5.07, 5.06, 5.05, 5.04, 5.03, 5.02, 5.01, 5.00, 4.99, 4.98, 4.97, 4.96, 4.95, 4.94, 4.93, 4.92, 4.91, 4.90, 4.89, 4.88, 4.87, 4.86, 4.85, 4.84, 4.83, 4.82, 4.81, 4.80, 4.79, 4.78, 4.77, 4.76, 4.75, 4.74, 4.73, 4.72, 4.71, 4.70, 4.69, 4.68, 4.67, 4.66, 4.65, 4.64, 4.63, 4.62, 4.61, 4.60, 4.59, 4.58, 4.57, 4.56, 4.55, 4.54, 4.53, 4.52, 4.51, 4.50, 4.49, 4.48, 4.47, 4.46, 4.45, 4.44, 4.43, 4.42, 4.41, 4.40, 4.39, 4.38, 4.37, 4.36, 4.35, 4.34, 4.33, 4.32, 4.31, 4.30, 4.29, 4.28, 4.27, 4.26, 4.25, 4.24, 4.23, 4.22, 4.21, 4.20, 4.19, 4.18, 4.17, 4.16, 4.15, 4.14, 4.13, 4.12, 4.11, 4.10, 4.09, 4.08, 4.07, 4.06, 4.05, 4.04, 4.03, 4.02, 4.01, 4.00, 3.99, 3.98, 3.97, 3.96, 3.95, 3.94, 3.93, 3.92, 3.91, 3.90, 3.89, 3.88, 3.87, 3.86, 3.85, 3.84, 3.83, 3.82, 3.81, 3.80, 3.79, 3.78, 3.77, 3.76, 3.75, 3.74, 3.73, 3.72, 3.71, 3.70, 3.69, 3.68, 3.67, 3.66, 3.65, 3.64, 3.63, 3.62, 3.61, 3.60, 3.59, 3.58, 3.57, 3.56, 3.55, 3.54, 3.53, 3.52, 3.51, 3.50, 3.49, 3.48, 3.47, 3.46, 3.45, 3.44, 3.43, 3.42, 3.41, 3.40, 3.39, 3.38, 3.37, 3.36, 3.35, 3.34, 3.33, 3.32, 3.31, 3.30, 3.29, 3.28, 3.27, 3.26, 3.25, 3.24, 3.23, 3.22, 3.21, 3.20, 3.19, 3.18, 3.17, 3.16, 3.15, 3.14, 3.13, 3.12, 3.11, 3.10, 3.09, 3.08, 3.07, 3.06, 3.05, 3.04, 3.03, 3.02, 3.01, 3.00, 2.99, 2.98, 2.97, 2.96, 2.95, 2.94, 2.93, 2.92, 2.91, 2.90, 2.89, 2.88, 2.87, 2.86, 2.85, 2.84, 2.83, 2.82, 2.81, 2.80, 2.79, 2.78, 2.77, 2.76, 2.75, 2.74, 2.73, 2.72, 2.71, 2.70, 2.69, 2.68, 2.67, 2.66, 2.65, 2.64, 2.63, 2.62, 2.61, 2.60, 2.59, 2.58, 2.57, 2.56, 2.55, 2.54, 2.53, 2.52, 2.51, 2.50, 2.49, 2.48, 2.47, 2.46, 2.45, 2.44, 2.43, 2.42, 2.41, 2.40, 2.39, 2.38, 2.37, 2.36, 2.35, 2.34, 2.33, 2.32, 2.31, 2.30, 2.29, 2.28, 2.27, 2.26, 2.25, 2.24, 2.23, 2.22, 2.21, 2.20, 2.19, 2.18, 2.17, 2.16, 2.15, 2.14, 2.13, 2.12, 2.11, 2.10, 2.09, 2.08, 2.07, 2.06, 2.05, 2.04, 2.03, 2.02, 2.01, 2.00, 1.99, 1.98, 1.97, 1.96, 1.95, 1.94, 1.93, 1.92, 1.91, 1.90, 1.89, 1.88, 1.87, 1.86, 1.85, 1.84, 1.83, 1.82, 1.81, 1.80, 1.79, 1.78, 1.77, 1.76, 1.75, 1.74, 1.73, 1.72, 1.71, 1.70, 1.69, 1.68, 1.67, 1.66, 1.65, 1.64, 1.63, 1.62, 1.61, 1.60, 1.59, 1.58, 1.57, 1.56, 1.55, 1.54, 1.53, 1.52, 1.51, 1.50, 1.49, 1.48, 1.47, 1.46, 1.45, 1.44, 1.43, 1.42, 1.41, 1.40, 1.39, 1.38, 1.37, 1.36, 1.35, 1.34, 1.33, 1.32, 1.31, 1.30, 1.29, 1.28, 1.27, 1.26, 1.25, 1.24, 1.23, 1.22, 1.21, 1.20, 1.19, 1.18, 1.17, 1.16, 1.15, 1.14, 1.13, 1.12, 1.11, 1.10, 1.09, 1.08, 1.07, 1.06, 1.05, 1.04, 1.03, 1.02, 1.01, 1.00, 0.99, 0.98, 0.97,	



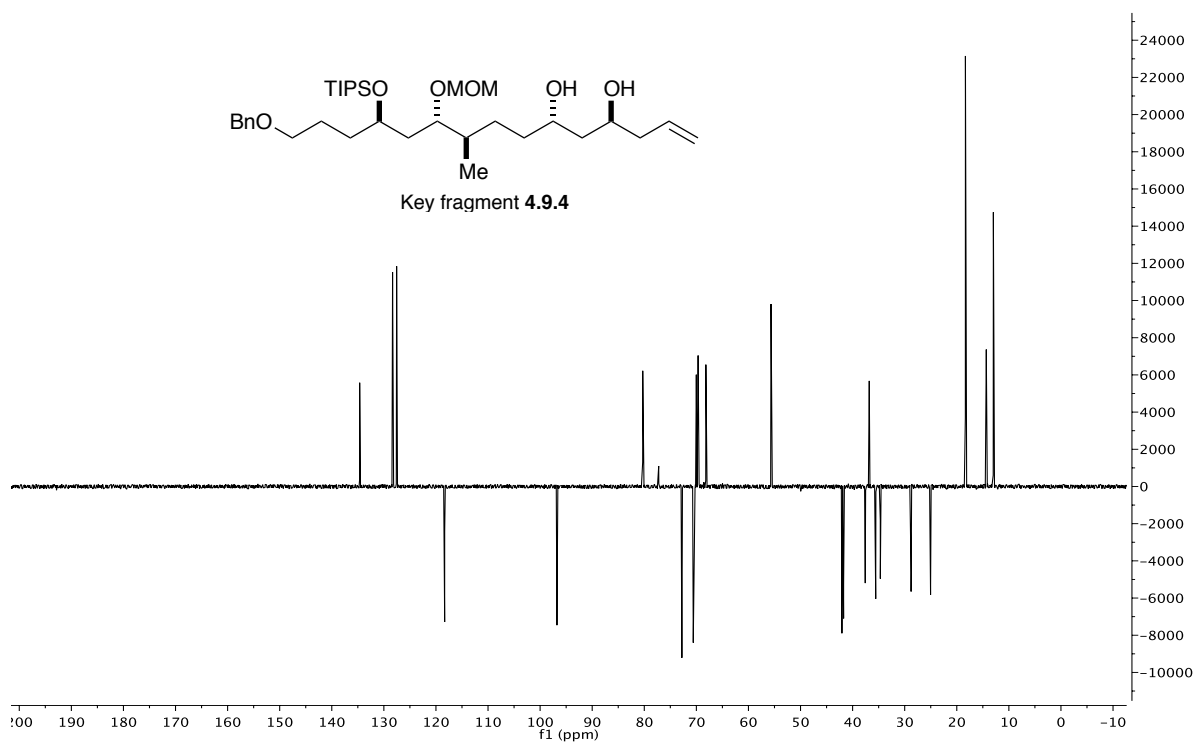
(1*R*,6*R*,8*S*)-8-((3*R*,4*S*,6*R*)-9-(benzyloxy)-4-(methoxymethoxy)-3-methyl-6-((triisopropylsilyl)oxy)nonyl)-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-ene 1-oxide (4.9d):



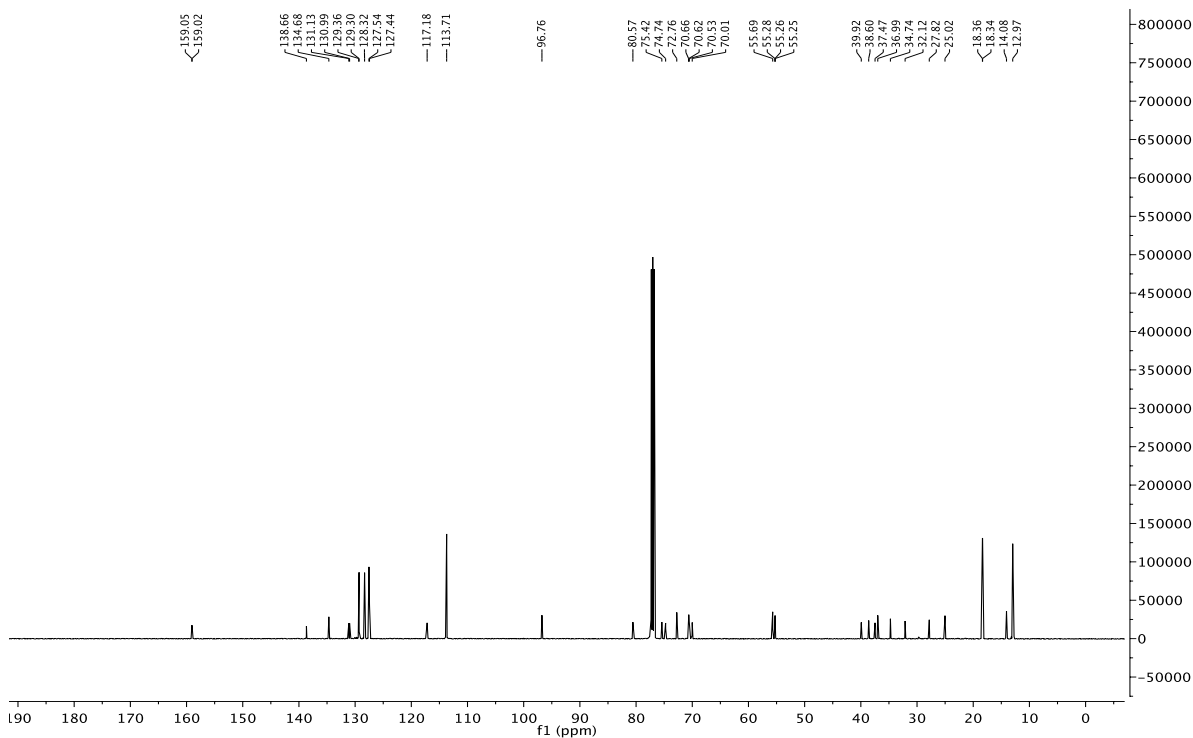
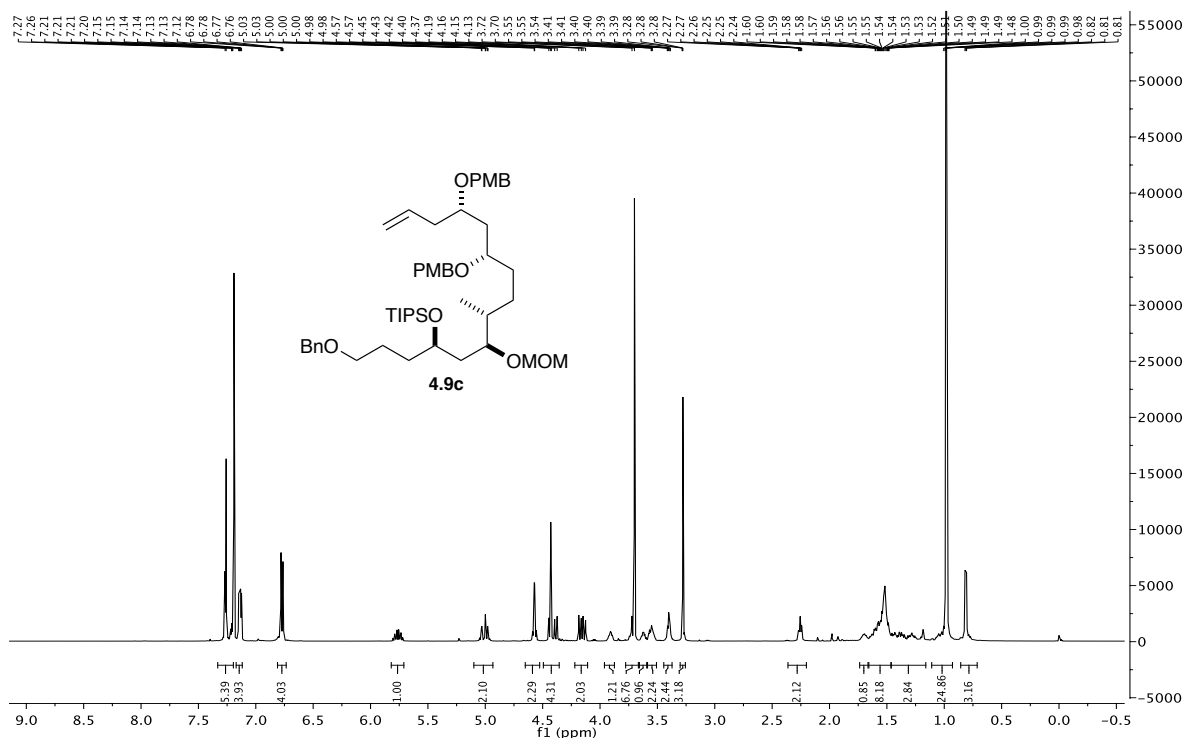
(1*R*,6*R*,8*S*)-8-((3*R*,4*S*,6*R*)-9-(benzyloxy)-4-(methoxymethoxy)-3-methyl-6-((triisopropylsilyl)oxy)nonyl)-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-ene 1-oxide (4.9d):



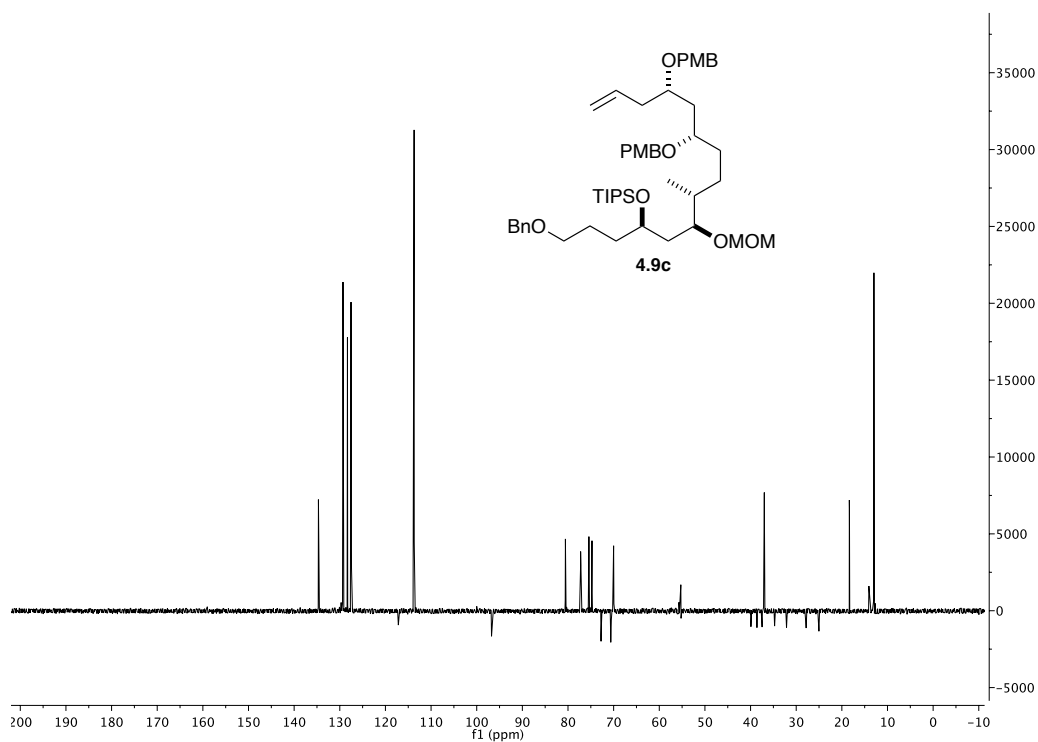
**propylsilyl)oxy)nonyl)-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-ene-1-oxide
(4.9d):**



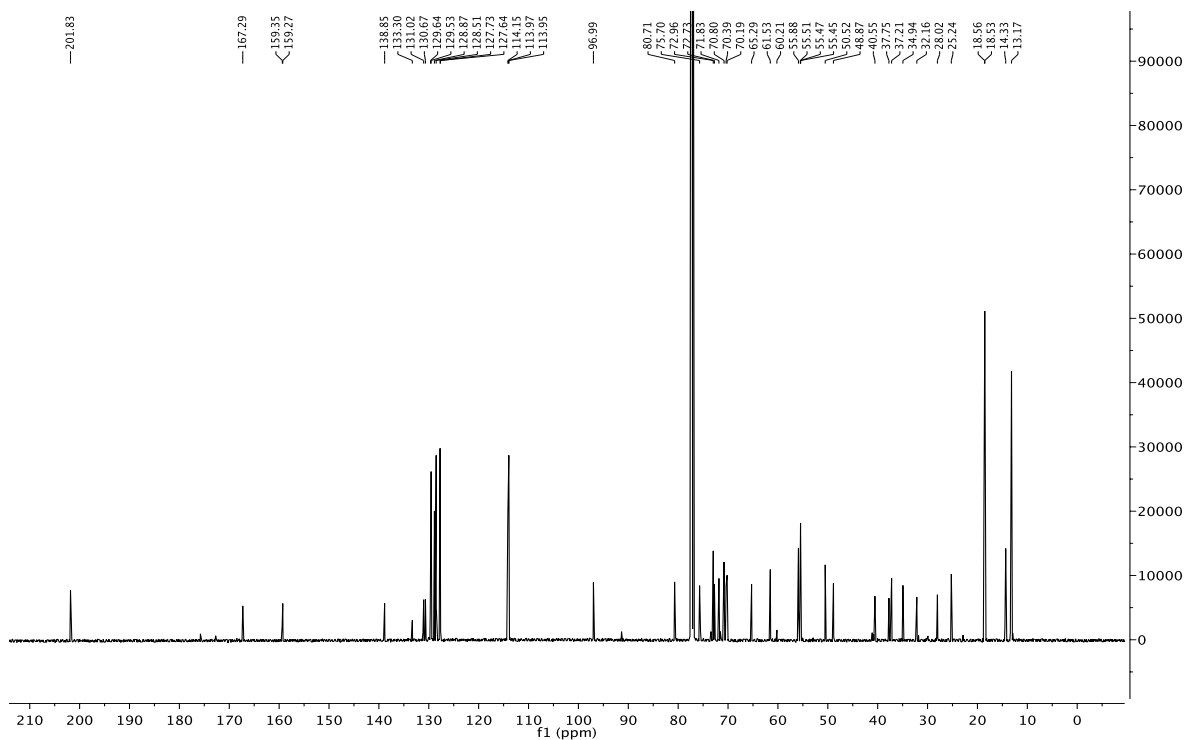
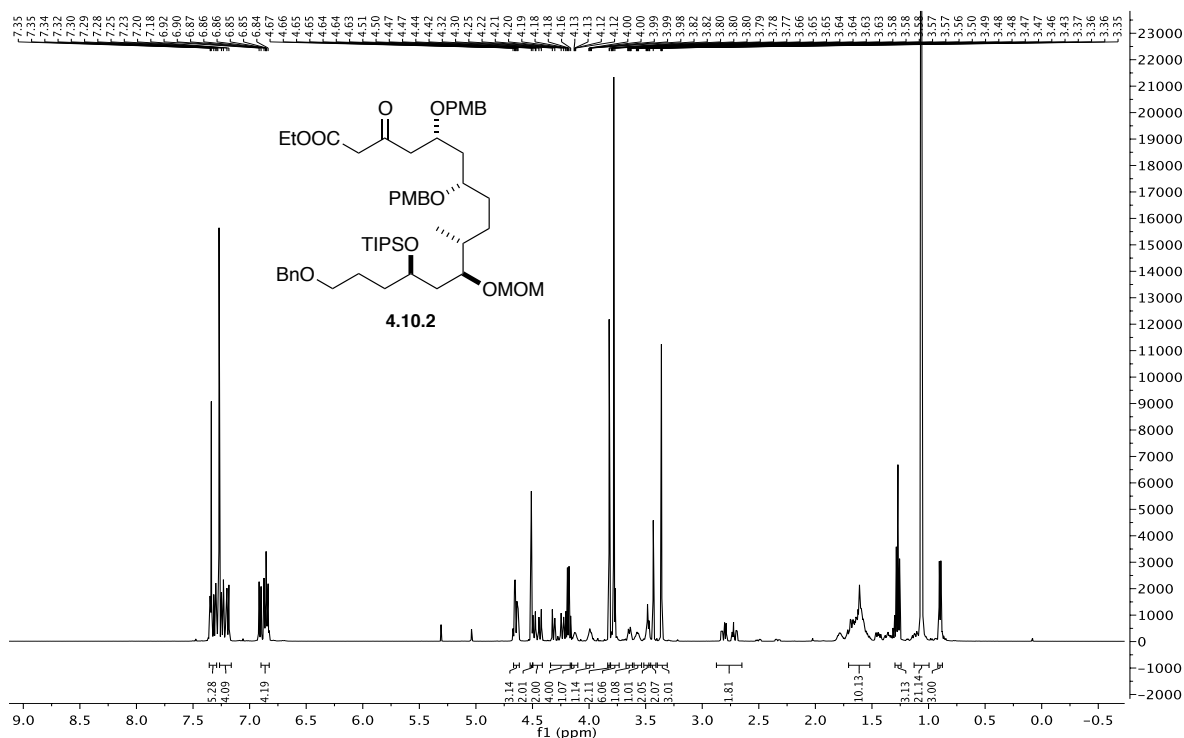
(5*S*,7*R*)-7-(3-(benzyloxy)propyl)-5-((2*R*,5*S*,7*S*)-5,7-bis((4-methoxybenzyl)oxy)dec-9-en-2-yl)-9,9-diisopropyl-10-methyl-2,4,8-trioxa-9-silaundecane (4.9c):



(5*S*,7*R*)-7-(3-(benzyloxy)propyl)-5-((2*R*,5*S*,7*S*)-5,7-bis((4-methoxybenzyl)oxy)dec-9-en-2-yl)-9,9-diisopropyl-10-methyl-2,4,8-trioxa-9-silaundecane (4.9c):



(5*R*,7*S*,10*R*,11*S*,13*R*)-ethyl-16-(benzyloxy)-5,7-bis((4-methoxybenzyl)oxy)-11-(methoxymethoxy)-10-methyl-3-oxo-13-((triisopropylsilyl)oxy)hexadecanoate (4.10.2):



(5*R*,7*S*,10*R*,11*S*,13*R*)-ethyl-16-(benzyloxy)-5,7-bis((4-methoxybenzyl)oxy)-11-(methoxymethoxy)-10-methyl-3-oxo-13-((triisopropylsilyl)oxy)hexadecanoate (4.10.2):

